Studies of auditory hallucinations using functional magnetic resonance

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Investigating Auditory Hallucinations in Schizophrenia using Functional Magnetic Resonance Imaging

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Abstract

It has been postulated that auditory verbal hallucinations (AH) occur when one's own verbal thoughts are not recognised, and are misinterpreted as belonging to another. The neurophysiological basis of this cognitive model of auditory verbal hallucinations can be examined using functional neuroimaging. I have sought, firstly, to identify the regions of the brain activated during AH; secondly, to investigate the functional anatomy of the processing of inner speech in normal volunteers and finally to examine the relationship between these areas and those implicated in inner speech processing in patients with schizophrenia prone to experience auditory hallucinations.

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Chapter 1

Introduction

Auditory Verbal Hallucinations

Auditory hallucinations (AH) are perceptions of external speech in the absence of a stimulus and occur frequently amongst psychiatric patients, being most common in schizophrenia, and are often described as "voices". A review of 16 studies (Slade and Bentall 1990) found an average prevalence of 60% for AH in patients with a diagnosis of schizophrenia (range 25-94%). AH may also occur in healthy individuals with surveys estimating lifetime prevalence rates of 10-39% in the general population (McKellar 1968, Posey and Losch 1983, Bentall and Slade 1985, Tien 1991). These surveys also suggest that non-psychotic subjects report having greater control over the experience, than those with psychosis, and that their hallucinations are usually less enduring.

Patients usually describe the hallucinations of speech as distressing, consistent with evidence that the commonest hallucinated utterances are abusive terms (Nayani and David 1996). The risks associated with auditory hallucinations were highlighted by Falloon and Talbot (1981) who found that more than a quarter of their schizophrenic patient sample had made a serious suicide attempt in response to AH. AH are usually treated with antipsychotic medication, but in 25 to 30% they are refractory to traditional antipsychotic drugs (Meltzer 1992, Kane et al 1988); there is insufficient experience of the effects of the atypical antipsychotics, with the exception of clozapine (Kane et al 1988), to suggest any preferential effects on AH.

Aetiological Theories

First I will briefly consider theories proposing mechanisms for AH; for a more comprehensive review of the aetiology of AH the reader is referred to Bentall (1990).

Lesion Studies

"Organic" conditions associated with AH can provide clues to the neural regions, which may generate AH. Temporal lobe lesions may lead to auditory hallucinations (Perez et al 1985, Penfield and Jasper 1954). However, brain stimulation experiments have failed to provide a convincing model of "functional" auditory hallucinations, as

the complex auditory verbal hallucinations characteristic of schizophrenia are rarely evoked (Penfield and Perot 1963).

Some authorities have implicated abnormalities of hemispheric lateralisation, with some emphasising the role of the left cerebral hemisphere (Flor-Henry 1986), others the right hemisphere (Cutting 1990) and yet others, inter-hemispheric communication (Green 1978). A study by Feinstein and Ron (1990) found no association between any particular site of brain pathology and psychotic experiences in patients seen at a specialist neurological hospital. Carter et al (1996) reported on the performance of 23 unmedicated schizophrenic patients compared to age and sex matched controls on the local/global differentiation task, which is sensitive to differences in right and left hemisphere processing. Their results suggested that patients were impaired in perception of the local compared to global tasks, demonstrated by slower response times to discrimination of smaller letters (local) making up larger letters (global); this was a reversal of the normal response pattern and was correlated with the severity of AH. This study supports the association between left temporal lobe abnormalities and AH, as attention to local aspects of a stimulus is lateralised to the left hemisphere. Similarly, when a dichotic listening task was administered to hallucinating and non-hallucinating psychotic patients, the hallucinating (but not the non-hallucinating) patients failed to show the expected right ear advantage (Green et al 1994). Ear asymmetry did not change whether the patient was hallucinating or not hallucinating; the authors concluded that enduring left temporal cortical abnormality may predispose patients to AH.

The case in favour of right hemisphere involvement in schizophrenia and AH has been reviewed by Cutting (1990, 1994). The major tenets of this argument are that a) the right hemisphere is associated with the recognition of rhythm or prosody and emotional aspects of language; and b) a dysfunctional right hemisphere will contribute to a failure to recognise the prosody and emotional aspects of an individual's own inner speech resulting in the experience of AH.

Cognitive Theories

Inner speech disorder is implicated in the pathogenesis of AVH by many of the current neuropsychological theories. Frith and Done (1988) suggested that there are

two types of stimuli; the first is external and has an impact via sensory organs, while the second is internally generated from planned or willed action. They propose that the latter, i.e. internal monitoring of willed action, is defective in psychotic illness, so that, in the case of AH, patients experience internally generated thoughts as externally generated. Similarly, David (1994) has hypothesised that AH may arise from a disturbance of the connection between the auditory analysis system ("inner ear") and phoneme output ("inner voice") leading to inner speech being misinterpreted as externally produced speech. Hoffman (1986) suggested that, in schizophrenia, inner speech be subject to discourse planning disruption, which produces unintended verbal images, experienced as hallucinations. In support of this hypothesis he demonstrated discourse planning disruption in external speech of patients with schizophrenia and a positive correlation between speech disorder and AVH. In hallucinating patients who lacked formal thought disorder, he hypothesized that these patients cope with discourse planning difficulties by reducing the complexity of their speech. Bentall (1990) considers that the ability to discriminate between external and internal, or real and imaginary, sources is a metacognitive skill; he hypothesised that some individuals undergo a "criterion shift" making them liable to interpret internal sources of stimulation as external. This notion is supported by evidence that hallucinating patients make hasty and overconfident judgements about the source of their perceptions (Alpert 1985, Heilbrun and Blum 1984), and that when their voice is distorted as part of a feedback process, they are more likely than normals to attribute the voice to another (Cahill et al 1997, Johns and McGuire 1999). It is probable that these different theories may both be relevant but operating at different levels, so there may be an element of dysfunction within the systems responsible for (automatic) self-monitoring of language as suggested by Frith and Done (1988) and David (1994) but that this is exacerbated by defects in a more (conscious) judgment about the veracity of the experience, following Bentall (1990).

An Integrative theory

Slade and Bentall (1990) presented a five-factor theory of hallucinations, incorporating many of the ideas discussed above. They propose that defective monitoring and reality discrimination may not be the sole factors in psychological explanations of AH, emphasising the potential contribution of arousal, cognitive deficits, environmental stimulation, reinforcement and patient's expectations.

However, it may be that these latter factors operate through an effect on self-monitoring or reality discrimination. For example, patients seem to be more likely to mis-identify their own distorted speech when the spoken words are emotional rather than neutral (Johns & McGuire, 1999).

Structural Neuroimaging

Structural imaging studies provide conflicting results about the role of speech areas in the pathophysiology of schizophrenia in general, and of AH. A recent meta-analysis of regional brain volumes in schizophrenia (Wright et al 2000) demonstrated a reduction in mean cerebral volume (patients had 98% when control subjects had 100%), with increased mean ventricular volume (126%). Regional structural differences included bilaterally reduced volume of medial temporal structures (amygdala 91%, hippocampus 93% and parahippocampal gyrus 92%), with less significant reductions in volumes of the left sided frontal (95%) and lateral temporal (93%) cortices.

Volumes of selected brain regions were suggested to be related to positive symptomatology in a study by Maher et al. (1998) which reported reduction of the normal hemispheric asymmetry of the frontal,and temporal lobes, and positive correlation with the early age of onset of the illness. However, in another study with a large sample size (Cowell et al., 1996) hallucinations and delusions did not correlate with the frontal or temporal lobe volume; in a third study with a similar sample size, the left temporal lobe volume reduction correlated positively with the severity of negative symptoms but not with the hallucinations score (Turetsky et al., 1995). Other studies have reported a reduction of the volume of the STG bilaterally (Barta et al., 1990) or on the left side (Shenton et al., 1992). The first study found positive correlation between the severity of hallucinations and volume reduction of the left STG. This finding was replicated once (Flaum et al., 1995). However, in other studies, STG volume did not differ between hallucinating and non hallucinating schizophrenic patients (DeLisi et al 1994; Havermans et al 1999), or between schizophrenics and normal controls (DeLisi et al 1994; Havermans et al 1999). The volume of the left anterior STG has been negatively correlated with the severity of hallucinations in one study (Levitan et al., 1999), while Rajarethinam et al., (2000), showed only a trend for negative correlation. However, Chua et al (1997) found that

hallucinations and delusions did not correlate with the gray matter volume in any brain region and similarly, a recent study of 74 male patients with schizophrenia failed to find any reduction in structural asymmetry of the sylvian fissure or planum temporale, or any association with propensity to experience auditory hallucinations (Shapleske et al 2001). Therefore conclusive evidence about associating AVH with structural abnormality of the speech perception area is lacking. Structural imaging yields contradictory results about the abnormality of the speech perception area (STG or planum temporale) in schizophrenia and when abnormality was found it was correlated with different symptoms (hallucinations or thought disorder).

Abnormalities in corpus callosum (CC) morphology in the schizophrenia literature have been equivocal, with initial claims of larger CC area in schizophrenia, based on post-mortem studies, failing to attract consistent support from in-vivo magnetic resonance imaging (MRI) studies, which instead point to a generalized reduction in cross-sectional area compared with controls (see Woodruff et al., 1995 for a systematic review). Methodological differences were cited as a major reason for the inconsistencies in the literature. One frequently identified problem within schizophrenia research in general is that the diagnosis covers a heterogeneous range of signs and symptoms and that this might obscure an association between a given biological parameter and a specific deficit, dimension, or in even symptom of the disorder. In relation to CC research, Gunther et al. (1991) found that Type 2 patients (i.e., those with predominately negative symptoms) had smaller CCs than Type 1 patients (those with predominately positive symptoms). This has been replicated by Tibbo et al. (1998), who reported that the decrement in CC size was related to the severity of negative symptoms. A more recent study in 71 subjects with schizophrenia has suggested there was no major morphological abnormality of the corpus callosum in schizophrenic patients, or any specific relationship to AH (Rosselll et al 2001).

Functional Neuroimaging

Language processing

Before going on to review neuroimaging studies of AVH, I will briefly describe the functional neuroanatomy of language processing in normal subjects. The earlier neurological models of language were based on lesion-models based largely on the observations of Broca (1861), Wernicke (1874) and Lichtheim (1885). These

proposed that speech (input) was experienced via the primary auditory cortex and processed in Wernicke's area (the left posterior superior temporal cortex); subsequent speech output required communication with Broca's area (the third frontal convolution of the frontal lobe) via the connecting white matter tracts (the arcuate fasciculus) and then onto the motor cortex for articulation. However, lesion studies seldom conform to functional neuroanatomical systems and cannot distinguish whether the lost function is associated with the damaged area or its subsequent connections; one cannot say that the damaged region was sufficient for, or uniquely related to that function. Thus, functional neuroimaging is complementary in identifying a more complete set of regions associated with a task while lesion models identify regions or connections, which are necessary for the particular task.

A review of functional imaging studies of language (Price 2000) concluded that auditory processing of speech input (hearing speech versus non-speech noise) is associated with activation of the bilateral superior temporal gyri. Accessing the meanings of words activates the left posterior middle temporal, and bilateral posterior temporoparietal and anterior inferior temporal cortices. Speech output (word repetition versus passive listening) is associated with activation in the posterior superior temporal sulci (non-semantically mediated speech), the left posterior inferior temporal cortex (involved during lexical, sematically mediated speech output) and the articulatory planning via the posterior part of Broca's area (pars opercularis and anterior insula), and the bilateral sensorimotor cortex. Additional activation was evident in the supplementary motor cortex and anterior cingulate gyrus, thought to be associated with initiation and planning of speech. It is clear that functional neuroimaging has served to refine the earlier neurological model, while keeping the basic framework. The additional information relates to the upper bank of the posterior superior temporal cortex equating to Wernicke's area; articulatory planning subserved by the anterior insula/pars opercularis (rather than the third frontal convolution); the angular gyrus was associated with semantic associations; and the meanings of words associated with the left inferior and middle temporal cortices.

Auditory Hallucinations

Neuroimaging has allowed the functional activity associated with AH to be investigated, permitting some of the theories listed above to tested. McGuire et al

(1993) first used Single Photon Emission Tomography (SPET) to study the areas activated during auditory hallucinations. Patients with schizophrenia were scanned twice, first whilst actively hallucinating and then at a later date when not hallucinating. The results showed increased blood flow in the left inferior frontal region (Broca's area) during hallucinations, thus implicating language production areas in the experience of AH. Subsequent SPET and Positron Emission Tomography (PET) studies have compared neural activation during auditory hallucinations while patients were required to signal the presence of hallucinations, demonstrating activation of the temporal cortex (Suzuki et al 1993), anterior cingulate gyrus (Cleghorn et al 1992) and subcortical regions including the thalamus, striatum and cerebellum (Silbersweig et al 1995). Other studies correlated resting state blood flow with clinical ratings of hallucinations to demonstrate associated activity within the parahippocampal region (Liddle et al 1992).

More recent work using functional magnetic resonance imaging (fMRI; Dierks et al 1999, Lennox et al 1999) required subjects to press a button when experiencing AH, (as well as experiencing the background noise associated with the fMRI scanning). This suggests that studying AH while they are being experienced is practicable with fMRI, but the impact of scanner noise and requirement for signalling, on these findings, is unclear. Overall, neuroimaging studies of active auditory hallucinations (McGuire et al 1993, Silbersweig et al 1995, Woodruff et al 1995, Dierks et al 1999) have typically reported activation in one or two brain regions, with different studies highlighting the involvement of different areas.

Abnormalities within Language Processing

Studies of intrinsic word generation using PET suggest that there may normally be a reciprocal relationship between activity in the left prefrontal and temporal cortices (Friston et al 1991; Frith et al 1995; Warburton et al 1996). Electrophysiological recordings in man indicate that neuronal activity in the temporal cortex is powerfully modulated by speech generation, and is more responsive to externally generated speech (Creutzfeldt et al 1989). This modulation with vocalisation can precede articulation by hundreds of milliseconds, suggesting that it may be related to the intention to speak, rather than articulation per se. Signals from regions concerned with

language articulation may thus inform temporal areas of impending language output, so the subsequently perceived speech is recognised as self generated.

Previous work using SPET and PET, has examined the neural correlates of cognitive processes putatively relevant to auditory hallucinations (McGuire et al 1995, 1996a). In normal subjects, the covert articulation of words is associated with activity in the left inferior frontal (LIF) region. Imagining another's voice saying the same kind of sentences is thought to require greater monitoring of inner speech and activates the supplementary motor area (SMA) and the left temporal cortex (McGuire et al 1995), in addition to the LIF region. When patients who are prone to second person hallucinations imagine sentences spoken in another's voice, the activation of the supplementary motor area and left temporal cortex is reduced, despite normal activation of the LIF region, relative to patients with no history of hallucinations and controls (McGuire et al 1996a). Abnormal activation in these areas is interesting, as they may play a role in internal 'inspection' of imagined speech, a form of verbal self-monitoring. Studies using fMRI suggest that the response of the right temporal cortex to speech may be reduced when patients are concurrently experiencing AH (Woodruff et al 1997). This suggests that auditory hallucinations and external speech compete for processing sites within the auditory cortex. Similar findings have been demonstrated by structural studies, which have demonstrated fronto-temporal dissociation in volumes of particularly prefrontal and superior temporal cortices (Woodruff et al 1997).

Aims of the Thesis

In this thesis I aim to use functional magnetic resonance imaging to examine the pathophysiology of auditory verbal hallucinations and the relationship of the latter to inner speech. I propose to test the hypothesis that AH arise through defective communication between brain areas involved in the generation and perception of language.

The first experiment sought to capture the pattern of neural activity while patients with schizophrenia were actively experiencing hallucinations (Chapter 3). The subsequent experiments examined activity in the brain regions associated with language generation and perception (the cognitive processes thought to be related to

auditory verbal hallucinations) as the form and rate of speech were experimentally manipulated. These experiments required healthy subjects to covertly generate speech, either in a different form or at a different rate, varying the demands on verbal self-monitoring (Chapter 4 and 5). These tasks were then examined in patients with schizophrenia who were prone to auditory hallucinations (Chapter 6 and 7).

Chapter 2

Measurement of Neural Activity using functional Magnetic Resonance Imaging

Background

Since the first human brain magnetic resonance (MR) images in the late 1970s the major focus of the technique has been on probing the anatomy and pathology of the central nervous system. Because the method can be made highly sensitive to flow, many groups, even at this early stage, also postulated extending the potential of MRI to interrogate brain physiology. Observing such changes was, however, limited to those in large vessels, and detection of "changes in blood supply in accordance with local variations of functional activity" (Roy and Sherrington, 1980) was prohibited by the need to acquire data for a minimum of several minutes.

Brain tasks are, by definition, often short-lived and the brain deals with many simultaneous sensory inputs, which may vary rapidly over time. Hence in order to achieve MR images reflecting brain function, one must perform extremely rapid MR image acquisition. Conventional MR systems have, in the past, taken several minutes to acquire information from any one anatomical location. To monitor the effect of rapid bursts of neuronal activity in functional MRI, the temporal resolution has to be improved to a maximum collection time of a few seconds. Fast MRI with conventional hardware has been achieved using fast gradient echo techniques with such acronyms as FLASH, SPGR, FISP, PSIF AND SSFP (for a review of fast imaging methods, see Wehrli, 1990).

However, arguably the best method available for collecting functional MR data is the echo planar imaging (EPI) technique. EPI is an ultra-fast, snapshot MR imaging method which allows capture of a full, single slice image after the application of only one radiofrequency pulse in a total acquisition time of less than 100 ms. Nevertheless, EPI has two major disadvantages 1) the need for a wide receiver bandwidth which leads to a reduction in signal-to-noise ratio and 2) the requirement to sample data for long acquisition times after each excitation which can lead to increased image distortion due to a higher sensitivity to magnetic field inhomogeneity. Despite the

implementation of field mapping and subsequent correction algorithms, the configuration of the object itself introduces magnetic field variations due to discrepancies in magnetic susceptibility between air, bone and the tissues of interest. At the higher magnetic field strengths necessary for functional MRI, signals from such boundaries, for example, the base of the frontal lobes above the paranasal sinuses and near the cerebellum can be grossly reduced, increased or displaced, in EP images.

BOLD Magnetic Resonance Imaging

This method relies on a natural change in the magnetic properties of the blood during neuronal activity. In 1936, Pauling noted that the magnetic susceptibility of haemoglobin and deoxyhaemoglobin differed slightly (Pauling and Coryell, 1936) and Thulborn *et al.* (1982) demonstrated that the magnetic state of haemoglobin in red cells is strongly dependent upon oxygen saturation. Deoxygenated blood is considerably more paramagnetic than oxygenated blood (Weisskoff and Kiihne, 1992). Therefore the signal decay rate of deoxygenated blood is more rapid than that of its oxygenated counterpart.

The effects of blood oxygen on the relaxation time T_2^* were first reported in MR images of anaesthetized rats by Ogawa *et al.* (1990). Ogawa termed his experiment "BOLD" - blood oxygen level dependent imaging. These results were elaborated upon by Turner *et al.* (1991) who used gradient-echo, echo planar imaging to observe the time course of these oxygenation changes whilst an animal breathed an oxygen-deprived, nitrogen atmosphere. The spatial resolution was insufficient to depict individual vessels but the drop in MR signal during anoxia within regions of well-perfused grey matter was readily observed.

Following this initial work, Kwong and colleagues attempted a photic stimulation study using a simple gradient-echo EPI method and probing MR signal changes due solely to the endogenous BOLD mechanism (1992). An echo time (TE) of 40 ms and a repetition time (TR) of 3 seconds was used to obtain a 1 cm thick axial image through the primary visual cortex at an in plane resolution of 1.5 mm. Subjects viewed short, 30-second epochs of stimulus flashing LED goggles interspersed with equal periods of darkness. When the sum of the "off-state" images was subtracted

from that of those acquired during photic stimulation the resulting difference image depicted a signal increase of some 3% in the primary visual cortex. The MR signal increase reflects a reduction in deoxyhaemoglobin concentration following the hyperoxemia that is associated with increased neuronal activity. Therefore the brain receives a greater supply of oxygen than the required demand (Frostig *et al.*, 1990).

One feature that is apparent from these data is the strong but delayed correlation between the input stimulus and the MR response. The rise to maximum BOLD effect can be delayed by 5-8 seconds (Eden et al 1999), reflecting the haemodynamic origin of the change of signal, but significant signal intensity increases can be observed within a few seconds after the onset of the stimulus.

Care must be taken when interpreting changes in BOLD contrast with different methods. It has been suggested that a change in, for example, blood arterial oxygenation, volume and flow as well as haematocrit and tissue oxygen uptake may alter the extent of BOLD signal change (Turner et al 1994). One encouraging observation has been the potential for increased BOLD contrast at higher magnetic field strengths. Turner *et al.* (1993) have observed changes of up to 15% in the primary visual cortex when they repeated the photic stimulation described above at 4T. This improvement is due to an increased signal-to-noise ratio at the higher field strength and the substantially greater change in magnetic susceptibility due to larger, local magnetic field gradients. Conversely, this also leads to a potential for both increased loss of signal and greater image distortion near air/bone/tissue boundaries at higher fields.

Practical Issues in conducting fMRI studies

General Considerations

The same contraindications must be considered for an fMRI study as would apply to a patient presenting for a standard clinical MR examination. Over and above considerations of metallic implants, cardiac pacemakers, early pregnancy etc. one must also consider acoustic noise. FMRI experiments using either conventional or echo planar imaging techniques are amongst the noisiest MR examinations. It is therefore important to carefully protect the subjects' ears prior to commencement of the experiment. Similarly, one must be realistic about the type of fMRI experiments

involving auditory perception that can be carried out, a particular issue for auditory-verbal paradigms (Amaro et al 1999).

Many fMRI tasks involve the subject looking at either a video recording or computer projection onto a screen at the end of the magnet bore. Therefore good eyesight, or non-metallic glasses are often necessary. Contact lenses are considered a contra-indication for MR, and many units insist they are removed. Task complexity is also an issue. It is usually helpful if subjects have been able to practice the required task prior to their insertion in the magnet. However, the amount of practice and/or the level of training attained should be controlled, as this can affect the pattern of activation (Petersen et al, 1998).

Subject Motion

One of the greatest practical concerns in fMRI studies is subject motion. All manner of devices to minimise such movement, including American football helmets and bite-bars, have been tried, but studies conducted at the Maudsley Hospital over a number of years indicate that subjects move least if 1) they are made comfortable using minimal binding straps and cushions, 2) the paradigms are kept as short as possible and 3) they are given the opportunity to rehearse the task beforehand.

Even in those cases where rigid fixation of the head has been employed, the most willing subject will typically move by at least a millimetre or so during the course of the study. Testing with interpolated data sets has confirmed that even if this movement is less than a pixel on direct image subtraction, a noticeable difference, which may initially be interpreted as brain activation, is still observed. Image realignment must therefore be performed. Early work involved monitoring movements of fixed markers during the course of an examination and then retrospectively applying the appropriate rotations and translations to the image series. More commonly, features within the images have been used to move the images back into register, post hoc (e.g. Tyszka *et al.*, 1994).

For successful implementation of all such image realignment algorithms, 3-dimensional (or multislice, 2-dimensional) image data must be acquired in order, as fully as possible, to characterise the 3 rotations and translations of a rigid body. Echo

planar imaging allows such data to be collected from the whole head in a typical total acquisition time of some 2-3 seconds. Even after perfect realignment movement related artifacts may still exist within the fMRI time series. This is because the MR signal in a particular slice is also dependent upon movement that occurred in previous scans, i.e. the spin excitation history and consequent variation in local saturation. By applying an autoregression-moving average model for the effects of previous displacements on the current signal, removal of this artifactual component can also be achieved (Friston *et al.*, 1996).

Image Acquisition

The fMRI data described in this thesis were acquired using gradient-echo, echo planar MR images using the 1.5 Tesla GE Signa System (General Electric, Milwaukee, WS, USA) retrofitted with Advanced NMR hardware (ANMR, Woburn MA, USA) based at the Maudsley Hospital, London. A quadrature birdcage coil encompassing the whole head was used for RF transmission and reception. In each of 14 non-contiguous planes parallel to the intercommissural plane, 100 T_2*-weighted MR images depicting BOLD contrast were acquired at a TE=40ms, TR=3000ms, an in-plane resolution=3mm, and slice thickness=7mm with 0.7mm gap. Head movement was minimised by foam padding within the head coil, and by placing a restraining band across the forehead. In the same session, a 43 slice, high resolution inversion recovery, gradient echo, echo planar image series of the whole brain was again acquired parallel to the intercommissural (AC-PC) plane with TE=40ms, TI=180ms, TR=16secs, in-plane resolution=1.5mm, slice thickness=3mm (8 data average). This latter data set allowed improved visualisation of the anatomy whilst maintaining any geometric distortion inherent within our EPI methodology. These echo planar images allowed direct superimposition of activated voxels from the time series without correction for geometric distortion which is necessary when such functional maps are registered onto conventional MR images.

Image Analysis

Movement Correction

Slight subject motion during MR image acquisition can cause changes in T_2*-weighted signal intensity unrelated to changes in the oxy-/deoxyhaemoglobin ratio.

The following procedure was applied to the data described in this thesis, in order to correct the effects of motion prior to any further analysis:

i) A base image of the mean signal intensity over time was created by averaging the 100 images acquired in each plane.
ii) The sum of absolute differences in grey scale values between the voxels of each match image and its corresponding base image was then computed.
iii) A non-linear search algorithm was used to estimate the extent of translation and rotation in 3 dimensions, which minimises the total difference between all match and base images.
iv) The match images were then realigned relative to the base image by tricubic spline interpolation.
v) The realigned, T_2*-weighted time series were then regressed on the concomitant and lagged time series of estimated movement at each voxel (Friston *et al.*, 1996).

The residual time series resulting from the last stage of this procedure were uncorrelated with estimated rigid body motion in 3D.

Having realigned each image and applied the appropriate intensity transformations to remove motion-related artifacts from the time series, there are a variety of statistical methods that can be applied to the data in order to extract areas of significant brain activation [see review Lange (1996)]. However, neuronal activation only induces small signal intensity changes (at 1.5T), which are often on a par with those fluctuations, which can be attributed to, for example, respiration, blood flow and cerebrospinal fluid motion. It is therefore essential to test the statistical significance of any changes, which appear to be associated with neuronal activation. Typically, significance tests are applied voxel by voxel with some correction for multiple comparisons, although initial studies employed region of interest methods (Ford and Holmes 1998). Early approaches compared the distributions of signal intensities with and without neuronal activation using Kolmogorov-Smirnov tests, t-tests or similar correlations between the time series and the boxcar function describing neuronal activation. However, these methods assume that the effect of neuronal activation on the signal is instantaneous, whereas it has been shown that the haemodynamic response to activation is gradual, reaching its maximum only after a delay of about 6s.

Haemodynamic response may be taken into account by regressing the observed time series on (or correlating it with) a reference vector representing the expected temporal response (Friston *et al.*, (1994); Bandettini *et al.*, (1993)). The simplest approach is to assume that the shape of this expected response is the same in all activated regions and to estimate it, for example, from the mean response in a region known to be activated. However, it has been shown that the response differs significantly between regions, particularly the delay to a maximum BOLD response relative to the onset of the stimulus (Bandettini *et al.*, 1995). Methods of estimating the shape of the temporal response include nonlinear estimation of the point spread function, which is assumed to yield the expected temporal response when convolved with the box car function and least squares fitting of linear regression models (Bullmore *et al.*, 1996a; Worsley and Friston, 1995) for example using sinusoidal terms. These more recent approaches also tackled the problem of temporal correlations in the time series, which had previously been ignored.

In summary, data processing requires good models and sophisticated statistical techniques to cope with the low signal to noise ratio, the regional heterogeneity of the haemodynamic response and the presence of temporal correlations in the signal. The variety of processing procedures and the dependence on both paradigm design and the MR experiment details currently makes direct comparison between the results from different neuroimaging centres difficult.

Time Series Analysis

There are a number of different approaches to image analysis. Two of the most widely used are Brain Activation Mapping (BAM) and Statistical Parametric Mapping (SPM). Both were employed in this thesis. They differ primarily in the specific method used to carry out the statistical testing.

Brain Activation Mapping uses the following approach: - the power of periodic signal change at the (fundamental) OFF-ON frequency of our stimulus (or task) is estimated by iterated least squares fitting a sinusoidal regression model to the motion-corrected time series at each voxel for all images. The model allows the shape and delay of the haemodynamic response to be estimated at each voxel, and takes account of temporal autocorrelations. The fundamental power quotient (FPQ = fundamental power

divided by its standard error) is then estimated at each voxel and represented in a descriptive parametric map. Each observed FMRI time series is then randomly permuted 10 times, and the FPQ estimated after each permutation. This results in 10 parametric maps (for each subject at each plane) of FPQ estimated under the null hypothesis that FPQ was not determined by periodic stimulation (Bullmore *et al.*, 1996a).

All parametric maps of FPQ are then registered in the standard space of Talairach & Tournoux (1993). This is done in two stages, using the realignment algorithms previously used for movement correction. First, the 14 slice set of FPQ maps derived from each subject is registered with that subject's high resolution EPI dataset; then registered and rescaled relative to a template image (previously obtained by averaging high resolution EPI datasets acquired from four normal volunteers in Talairach space). Identical transformations are applied to the randomised FPQ maps obtained for each subject. After spatial normalisation, the observed and randomised FPQ maps from each subject are identically smoothed with a Gaussian filter (SD = 3mm or 1 voxel), to accommodate variability in gyral anatomy and error of voxel displacement during normalisation. Generic activation is then robustly determined by computing the median value of FPQ at each voxel of the observed parametric maps, and comparing it to a null distribution of median FPQ values computed from the randomised parametric maps. If the observed median FPQ exceeds the critical value of randomised median FPQ, for a test of size $\dot{B}=2.5\times10^{-4}$, then that voxel is generically activated with probability of false positive activation=$\dot{B}$. At this level of significance testing, 5 voxels are expected to be 'activated' by chance over the whole median image.

Equivalence class testing (a standard algorithm used to classify or allocate voxels to a specific numbered cluster) is then used to determine the size and number of 8-connected voxel clusters in the observed and randomised images. The distribution of voxel cluster size in the randomised images is used to assign a probability under the null hypothesis to each voxel cluster in the observed image. For each voxel in the observed image, its probability under the null hypothesis in terms of time series activity is combined with its probability under the null hypothesis in terms of spatial clustering. Voxels with such a spatiotemporally combined probability of false

positive activation <0.0005 are regarded as activated, yielding a brain activation map. Finally, the generically activated voxels are coloured and superimposed on a high-resolution EPI data to create generic brain activation maps.

Some of experiments in this thesis were analysed using statistical parametric mapping software; SPM99 software (Statistical Parametric Mapping, The Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm) on a SPARC Ultra 10 workstation (Sun Microsystems, Palo Alto, CA) using MATLAB (version 5.3, The Mathworks Inc, Natick, MA). The main reason for using this different analysis software was that it permitted access and exploration of the time series within regions of interest, thus allowing elementary functional connectivity analyses (how the time series from different brain regions were related to one another). The SPM method does not vary significantly from the BAM approach described above, but employs a different method of statistical testing. SPM uses the general linear model but uses the theory of continuous random fields to make the data conform to a normal distribution, permitting examination using standard statistical tests such as t-tests, Ancova's and F-tests etc (as opposed to permutation/randomisation testing). Overall, using a similar p-value permits the results from both statistical packages to be compared with each other.

Chapter 3

Neural Activity During Auditory Hallucinations

Background

Previous neuroimaging studies have sought to "capture" the pattern of activity during auditory hallucinations by asking patients to signal when they occur (Silbersweig et al 1995, Lennox et al 1999, Dierks et al 1999), but the results were inconsistent. This may have reflected the confounding effects of signalling the presence of hallucinations, which can engage areas theoretically implicated in auditory hallucinations (Frith and Done 1989), as well as small numbers of subjects and the acquisition of a limited number of images per subject (Silbersweig et al 1995): most previous studies, [with a few exceptions Woodruff et al 1995, Dierks et al 1999; Lennox et al 1999], involved single photon or positron emission tomography (SPET or PET), which constrain the number of scans that can be safely acquired in each subject. Studies may have also have varied in terms of the clinical characteristics of the patients and the subtypes of hallucinations that were examined.

This chapter describes the use of a novel method that measures spontaneous neural activity using functional magnetic resonance imaging (fMRI) and permits the acquisition of a relatively large number of images in each subject, without the subject having to signal when auditory hallucinations occur. Moreover, while the scanner noise generated during conventional fMRI can itself activate auditory cortex (Bandettini et al 1998), the approach developed for this study allows activity during auditory hallucinations to be examined in silence. This "random sampling" method can be viewed as a variant of event-related fMRI (Buckner 1998) that measures the neural correlates of discrete cognitive events, (in this case spontaneous hallucinations), rather than the neural response to experimentally presented stimuli.

Methods

Subjects

Six male patients with schizophrenia and frequent auditory hallucinations were studied. Diagnosis was based on DSMIV criteria for schizophrenia (American Psychiatric Association 1994), a detailed clinical interview and review of their

hospital case notes. Patients were excluded if they had a history of head injury, neurological symptoms, speech or hearing difficulties, fulfilled DSM-IV criteria for abuse or dependence of any illicit drugs or alcohol during their lifetime, or any contraindications to MRI scanning, including metal implants and claustrophobia. They were recruited from wards and clinics at the Maudsley Hospital, London. Their mean age was 35 years (SD 11) with mean IQ 109 (SD 6), measured using the National Adult Reading Test (Nelson 1991;NART). All experienced intermittent and frequent, typically occupying a half of their waking hours, auditory hallucinations of fully formed speech, mostly of a derogatory nature. Two subjects reported exclusively second person hallucinations while the other four subjects described both second and third person hallucinations. The mean length of illness in the patients was 11 years (SD 8) and all were being treated with antipsychotic medication at the time of the study; five with atypical antipsychotics (Patient (Pt) 1 -clozapine 650mg and 1.5g sodium valproate daily; Pt2 and Pt3– olanzapine 20mg daily; Pt4 – olanzapine 30mg daily; Pt5 - clozapine 650mg and 1g sodium valproate daily), and one with a conventional antipsychotic (Pt6 – haloperidol injection 50mg monthly). All subjects provided written informed consent to enter the study, which had been approved by the Maudsley Hospital Ethics Committee.

Procedure

A 1.5 Tesla system was used to measure BOLD contrast during auditory hallucinations. Two paradigms were used: a) a novel random "sampling" method (Figure 3.1) and b) a more conventional "button-pressing" approach (Figure 3.2). The sampling method required subjects to lie at rest with their eyes closed. At randomly varied intervals of 30-60s they heard the noise generated by the acquisition of a single volume of fMRI data (duration 3 seconds). This served as an auditory cue for them to describe whatever they had been thinking or experiencing in the few seconds preceding the noise. They reported this verbally as soon as the noise stopped. Because there is typically a lag of 3-5 seconds between neural activity and the maximum BOLD signal (Eden et al 1999) (which reflects the local haemodynamic response to that activity- see Chapter 2), the image depicts the activity that was occurring a few, usually in the five, seconds before the onset of the cue. After providing a description,

Figure 3.1 The Random Sampling method of examining hallucinations

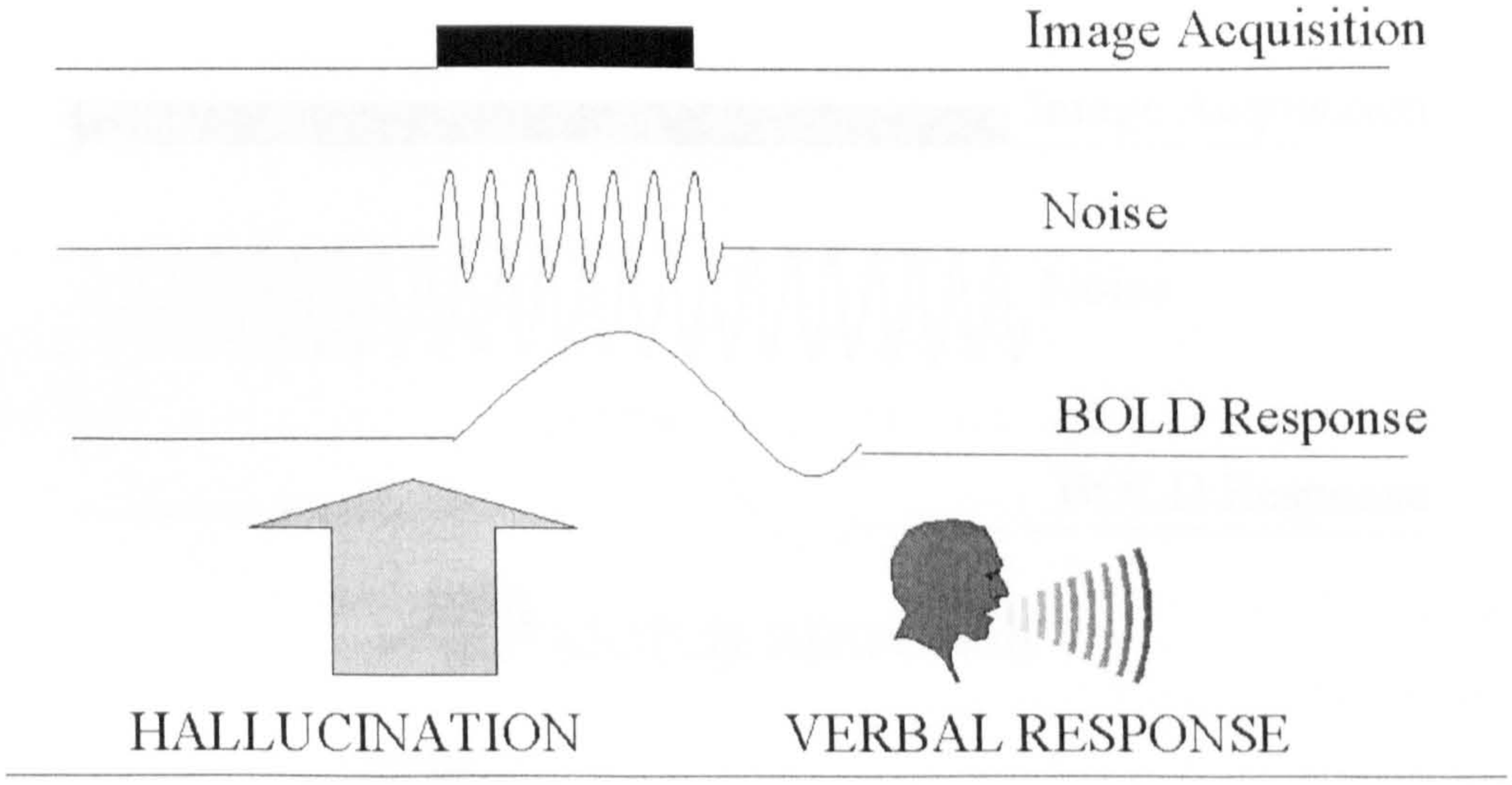
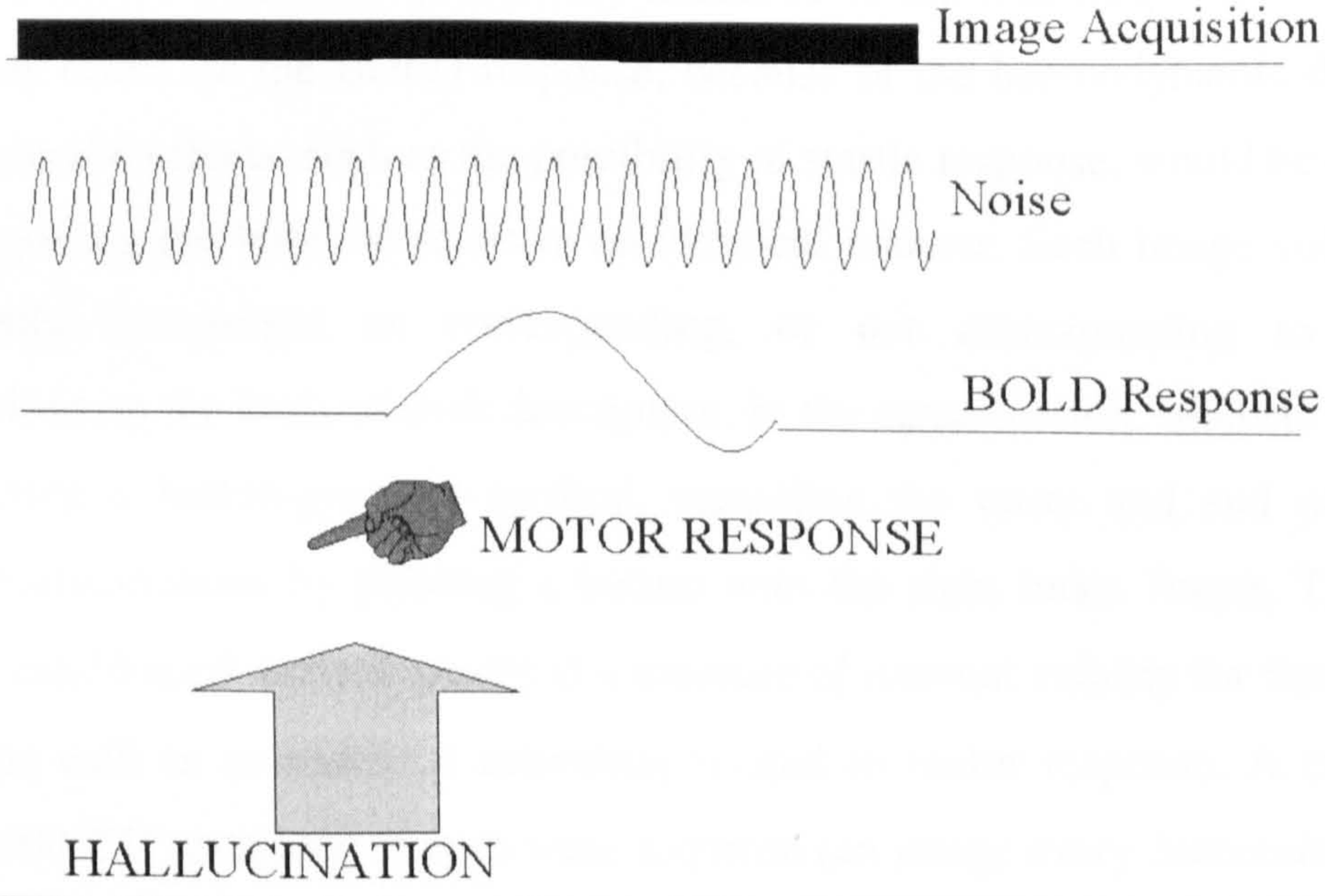


Figure 3.2 The Button Press method of examining hallucinations



subjects returned to the resting (but intermittently hallucinating) state and the procedure was repeated until a mean of 50 whole brain T2*-weighted images had been acquired from each subject. The choice of 30-60 second variation between scans was a pragmatic one to keep the total acquisition time to be between 60 and 90 minutes per subject, the maximum that patients were able to tolerate in one session (the individual scan time for 2 subjects was 60 minutes, 75 minutes for 2 subjects and 90 minutes for the other 2 subjects). Any influence of the scan noise itself is unlikely to have any effect on the BOLD response, because of the haemodynamic delay, and any non-specific effects, such as the possibility of startle response, would be cancelled out by acquiring the baseline scans in an identical manner. Each image volume was subsequently categorised as corresponding, or not corresponding to auditory hallucinations on the basis of each description. In the same session, subjects were also studied using a button-pressing method, signalling the onset and end of discrete auditory hallucinations by pressing a button with the right index finger. The use of this more established method provided a measure of internal validity for the sampling method, as well as an index of activation related to motor response. A continuous series of 100 T2*-weighted images were acquired (an image every 3seconds) over a 5 minute period, and the timing of the button press was used to indicate which portions of this block coincided with auditory hallucinations.

Image Acquisition and Analysis

Gradient-echo echoplanar MR images were acquired using a 1.5 Tesla GE Signa System fitted with Advanced NMR hardware and software. In each of 14 non-contiguous planes parallel to the inter-commissural (AC-PC) plane, 40 - 100 T2*-weighted MR images depicting BOLD contrast were acquired with TE = 40ms, TR= 3000ms, in-plane resolution = 3.1 mm, slice thickness = 7mm, slice = skip 0.7mm. Following the minimisation of movement related artifacts by realignment and regression (Brammer et al 1997) voxel-wise activation maps were constructed by computing the product moment correlation of the time series at each voxel (Bandettini et al 1993) with the reported occurrence of auditory hallucinations. Ten further maps were computed at each voxel after randomly permuting the pattern of auditory hallucinations reports. Following mapping of observed and randomised correlation data into standard stereotactic space (Talairach and Tournoux 1988), median observed and randomised maps were constructed. Foci of activation with a voxel-wise probability of type I error

of <0.0001 (at this level of significance one expects less than 1 random error voxel per slice of data) were identified by determining the critical threshold from the distribution of correlation coefficients computed following random permutation (Edgington 1980, Brammer et al 1997). In order to compare the activation with the two different methods of acquisition, the data from the two experiments were then combined and the correlation coefficients in all subjects, in both experiments, at each voxel in standard space were analysed using the linear model below. This identified effects that were dependent on, and independent of, the experimental condition (sampling or button press):

$$Corr_{i,j} = \beta_0 + \beta_1 E + e_{i,j} .$$

Where $Corr_{i,j}$ is the observed correlation coefficient for subject i in group j; β_0 is the overall mean, β_1 the difference in the mean correlation coefficient between the experiments, E is the classification variable coding experimental design and $e_{i,j}$ is an error term. This model was fitted to the Talairach transformed correlation coefficients obtained by random permutation of the time series (see above) as well as the correlation coefficients obtained by the analysis of the observed time series. Fitting this model to the randomised correlation data (across the two groups on a voxel-wise basis) permitted the construction of distributions of β_0 and β_1 under the null hypothesis that there was no experimentally determined response to the sampling or button press conditions. The null distributions of β_0 and β_1 were then used to determine the critical values of the two parameters for statistical significance at any required level of probability. We were primarily interested in differences due to the method of acquisition (sampling or button press) i.e. in estimating and testing experiment-independent effects (β_0). However, as β_0 is independent of β_1 a significant value of β_0 could arise principally due to a contribution from one of the experiments. For example, a large response in one experiment and a small one in the other may produce a mean value, which is significant but does not imply any constancy of responses in the two experiments. The inclusion of the $\beta_1$term in the model allows such responses to be identified and removed from the activation maps. Following this conservative correction of the data, significant effects were rendered onto a morphological template.

Results

Sampling Method

All six subjects experienced frequent auditory hallucinations when studied with the sampling method. They had a mean score of 57 (range 41-51) on the Brief Psychiatric Rating scale (BPRS;Woerner et al 1988), with all subjects scoring 5 or above on the auditory hallucinations item. A mean of 50 images (range 40-60) were acquired during the experiment and subjects reported hallucinations during a mean of 44% of scans (range 33%-60%). The sampling method revealed activation associated with auditory hallucinations in the inferior frontal gyrus/insula and middle temporal gyri bilaterally, particularly in the right hemisphere, where there was additional activation in the superior temporal gyrus, middle frontal gyrus, posterior parietal cortex, thalamus and inferior colliculus. Activation was also evident in the anterior cingulate gyrus, and in the left hippocampus and parahippocampal gyrus. These data are detailed in Table 3.1 and illustrated in Figure 3.3. As an index of the consistency of activation across subjects, significant right temporal activation was evident in four of the six individuals.

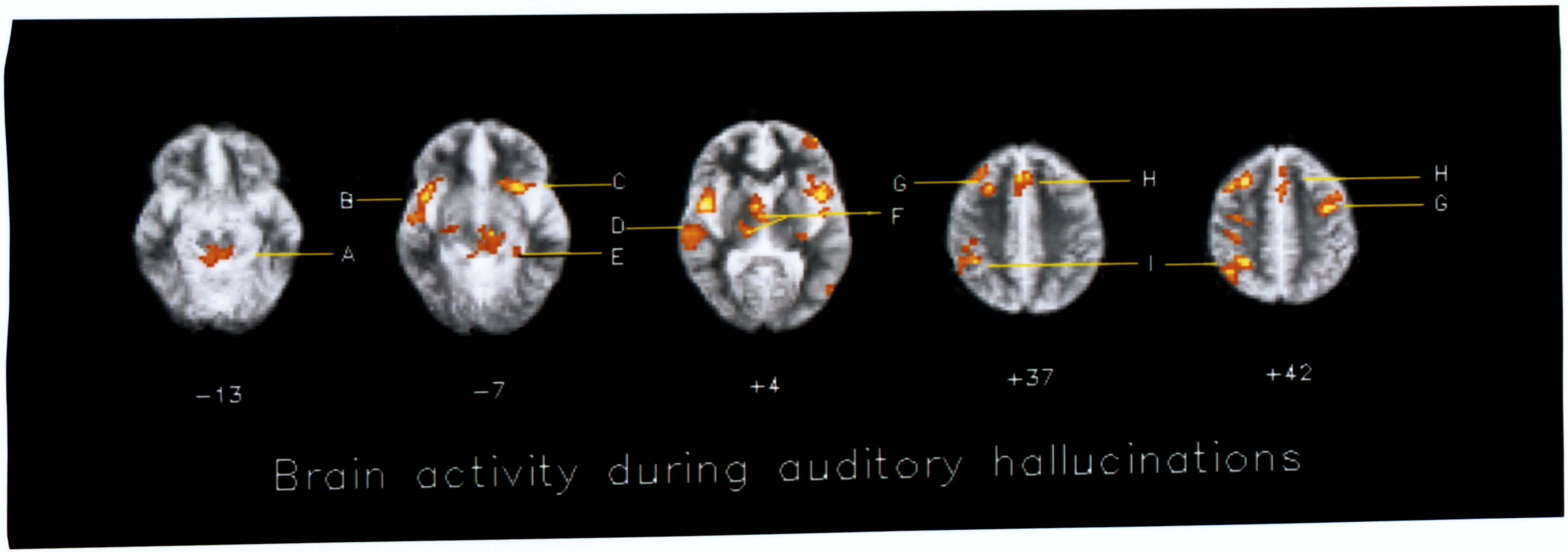
Button-press Method

Five of the patients reported auditory hallucinations during the button-pressing paradigm (hallucinating during a mean of 25% of scans; range 5%-52%), with the remaining subject reporting that the scanner noise interfered with the experience. There was no obvious periodicity in the hallucinatory activity of any individual patient. The button press method demonstrated significantly less activation of the inferior frontal and right lateral temporal gyri than with the sampling approach and there was no activation in the right middle frontal gyrus, thalamus or inferior colliculus (even at a liberal threshold of $p<0.01$). Conversely, only the button pressing method was associated with activation in the left primary motor cortex, and the right cerebellum and putamen (Table 3.2; Fig 3.4).

Overall, there were an insufficient number of events to examine the difference in activation between the different subtypes of hallucinations i.e second versus third person AH.

Figure 3.3 Group brain activation during random sampling of hallucinations.

Five transverse sections through the brain, at different levels relative to the intercommissural plane (mm), are shown. The right side of the brain is shown on the left side of each section. The coloured areas are regions that were activated during auditory hallucinations, with the foci of maximal significance shown in yellow. The main activations ($p<0.0001$) were in the right inferior colliculus (A), the right and left insula (B and C), the left parahippocampal gyrus (E), the right STG (D) and right thalamus (F). Activation was also evident in the middle frontal (G), and anterior cingulate gyri (H), and in the right inferior and superior parietal lobule (I).



Brain activity during auditory hallucinations

Table 3.1 Regions activated during random sampling of hallucinations (N=6)

Thresholded at p<0.0001

REGION (BA)	COORDINATES (X Y Z)			CLUSTER SIZE
L Anterior cingulate gyrus (BA 32)	-23	19	26	17
R Anterior cingulate gyrus (BA 32)	6	25	37	26
L Insula	-40	6	4	77
R Insula	43	8	-7	42
L Middle frontal gyrus (BA 9)	-35	-3	42	33
(BA 46)	-38	47	4	15
R Middle frontal gyrus (BA 8)	29	19	42	27
(BA 46/10)	38	39	20	38
L Inferior frontal gyrus (BA 44)	-43	8	9	77
R Precentral gyrus	38	-8	42	9
R Postcentral gyrus	38	-22	42	11
L Middle temporal gyrus (BA 39)	-49	-67	4	5
R Middle temporal gyrus (BA 21)	58	-33	-2	32
R Superior temporal gyrus (BA 22)	61	-22	4	38
R Inferior parietal lobule (BA 40)	40	-39	37	42
R Superior parietal lobule (BA 7)	29	-44	42	37
L Hippocampus	-26	-31	-2	8
L Parahippocampal gyrus (BA 35/36)	-23	-39	-7	7
R Thalamus (ventral anterior n)	9	-3	4	27
R Inferior colliculus	6	-39	-13	31

KEY: BA=Brodman Area; Cluster size=total number of activated voxels in region

Figure 3.4 Group brain activation during button press sampling of hallucinations.

Four transverse sections through the brain, at different levels relative to the intercommissural plane (mm) are shown. The right side of the brain is shown on the left side of each section. The areas coloured red are regions that were activated during auditory hallucinations (areas coloured blue are regions activated during non-hallucinating periods and are not discussed further). The main activations ($p<0.0001$), going from inferior to superior slices, were in the right inferior frontal gyrus/insula and the left middle temporal gyrus (-7mm), the bilateral insula, parahippocampal and superior temporal gyri and the left inferior frontal gyrus (+4mm), the left inferior frontal and precentral gyri (+31mm) and left middle frontal gyrus (+48mm).

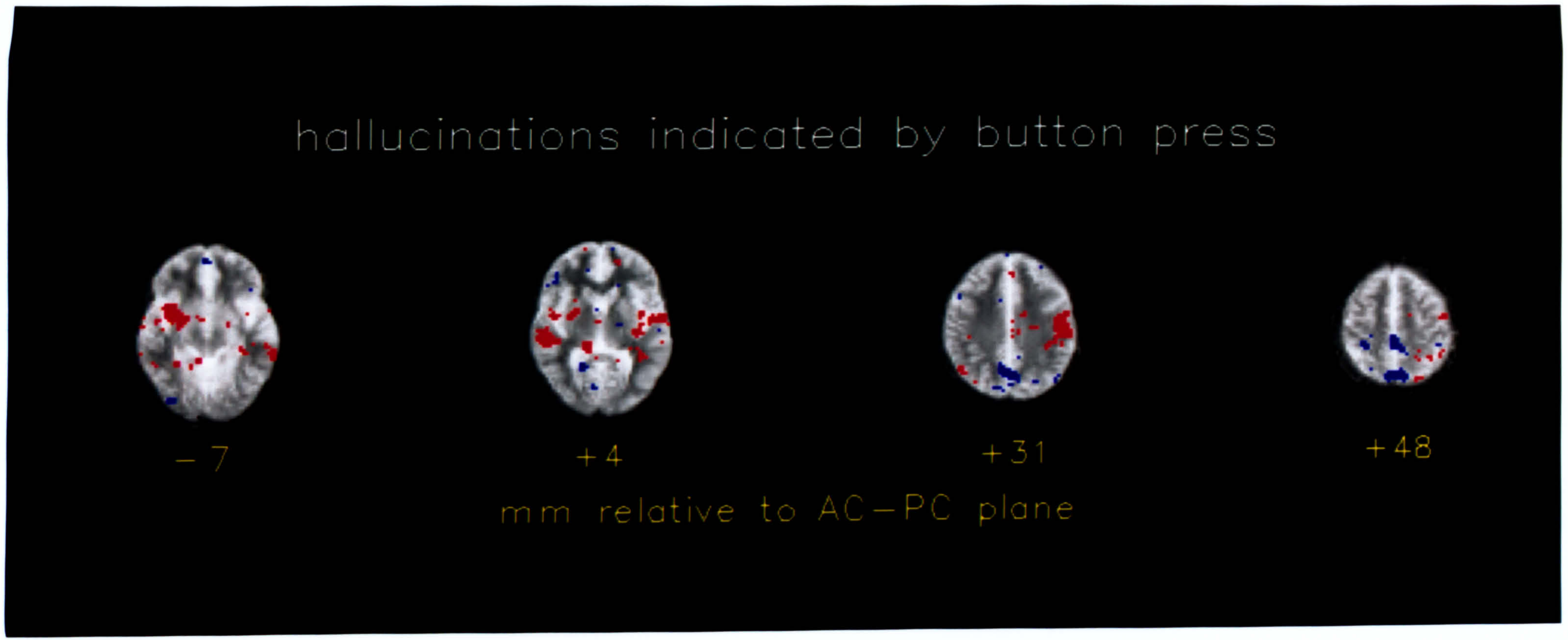

hallucinations indicated by button press
−7
+4
+31
+48
mm relative to AC−PC plane

Table 3.2 Regions activated during button press signalling of hallucinations (N=5)

Thresholded at p<0.0001

REGION (BA)	COORDINATES (X Y Z)			CLUSTER SIZE
R Frontal pole (BA 10)	12	50	15	29
(BA 9)	23	50	26	12
L Anterior cingulate gyrus (BA 24)	-20	22	20	91
L Middle frontal gyrus (BA 9)	-35	6	37	36
	-14	39	31	12
L Insula	-35	-6	4	7
R Insula	32	3	-7	9
L Inferior frontal gyrus (BA 44)	-35	8	31	18
L Precentral gyrus (BA 4)	-46	-8	31	18
	-40	-8	48	10
L Middle temporal gyrus (BA 21)	-52	-8	-13	30
	-61	-33	-7	17
L Superior temporal gyrus (BA 22)	-55	-8	4	12
R Superior temporal gyrus (BA 22)	49	-25	4	28
(BA 42)	35	-25	20	15
L Inferior parietal lobule (BA 40)	-46	-28	26	14
L Parietal operculum (BA 43)	-38	-11	20	25
R Parietal operculum (BA 43)	49	-11	15	14
L Anterior cingulate gyrus (BA 24)	-20	-19	37	15
L Posterior cingulate gyrus (BA 29)	-6	-39	20	15
L Hippocampus	-32	-36	-2	19
L Parahippocampal gyrus (BA 35/36)	-26	-33	-13	24
	-12	-50	4	15
R Parahippocampal gyrus (BA 30)	12	-36	4	7
R Anterior cerebellar cortex	29	-42	-24	39
Cerebellar vermis	-3	-47	-18	5
R Putamen	26	8	4	6

Discussion

A striking feature of this study was the identification of an extensive network of cortical and subcortical areas associated with auditory hallucinations; previous neuroimaging studies of auditory hallucinations have typically reported less extensive activation (Cleghorn et al 1992, Suzuki et al 1993, McGuire et al 1993, Silbersweig et al 1995, Woodruff et al 1995, Dierks et al 1999, Lennox et al 1999). Thus, earlier work using single photon emission tomography (SPET) linked auditory hallucinations with activation in the left inferior frontal cortex (McGuire et al 1993), while other studies, using both fMRI and PETimplicated the anterior cingulategyrus (Cleghorn et al 1992), the left (Dierks et al 1999, Suzuki et al 1993) and the right lateral temporal cortex (Dierks et al 1999, Woodruff et al 1995, Lennox et al 1999), the left parahippocampal region (Liddle et al 1992) and the thalamus, striatum and cerebellum (Silbersweig et al 1995). As all of these areas were activated in the present study, these apparently inconsistent findings may have resulted from identification of different elements of the same network. Most previous studies involved single photon or positron emission tomography (SPET or PET) that limits the number of images that can be safely acquired in each subject, and some examined a few selected regions of interest, as opposed to the entire brain.

Comparison of the two paradigms (one, which required subjects to signal the presence of auditory hallucinations, and one, which did not) clarified which activations were related to the act of signalling rather than to hallucinations per se. The areas which were exclusively activated with the button pressing method (the left precentral gyrus, the right cerebellar cortex and putamen) are normally engaged during voluntary movements of the right index finger (Rao et al 1996). The greater activation of the right middle and superior temporal gyri, thalamus and inferior colliculus with the sampling method may reflect the fact that with this paradigm neural activity was measured in the absence of background scanner noise, which may have obscured these responses when the button press method was used (Bandettini et al 1998, Hall et al 1999, Guimares et al 1998). This difference in activation is unlikely to have been a simple function of power, as the button press method involved a larger total number of scans. While there were significant differences in activation with two methods, there was also a considerable degree of overlap. Thus, both methods identified activation in the inferior frontal, premotor, inferior parietal and temporal cortex. The

engagement of these regions with the sampling method, in the absence of a motor response, is consistent with the notion that auditory hallucinations involve the processing of inner speech, which engages the same areas (Price et al 1996, McGuire et al 1996a). This finding is congruent with one of the most prominent cognitive theories of auditory hallucinations (Frith and Done 1989) that proposes that there are two types of perceptual experiences; the first is external and has an impact via sensory organs, while the second is internally generated as a consequence of planned or willed action. They believe that the internal monitoring of willed action is defective in psychotic illness, so that, in the case of AH, patients experience internally generated thoughts as externally generated. The left parahippocampal region also revealed activation, common to both methods, as reported in previous studies (Liddle et al 1992).

While imagining speech is associated with a marked activation in the supplementary motor area (SMA; McGuire et al 1996a), this region was only weakly engaged during auditory hallucinations. Conversely, auditory hallucinations were associated with activation in the left parahippocampal region, but this region is not activated when volunteers imagine alien speech (McGuire et al 1996). The SMA has been implicated in the deliberate generation of inner speech (McGuire et al 1996a, Curtis et al 1998), and lesions in this region are associated with the alien limb syndrome, in which the patient loses awareness that his movements are self-generated and attributes them to someone else (Gasquoine 1993). The paucity of SMA activation that we observed during auditory hallucinations might thus be related to a lack of awareness that inner speech has been generated (McGuire et al 1995), thought to be the critical deficit underlying auditory hallucinations (Frith and Done 1989). The left parahippocampal region is normally activated when subjects encounter unexpected stimuli (Stern et al 1996) and psychological models of self-monitoring propose that it is engaged when there is a mismatch between the perceived and predicted results of cognitive activity (Gray et al 1990). Data from previous neuroimaging studies have suggested that the left parahippocampal gyrus, ventral striatum and prefrontal cortex form a network of regions associated with AH (Liddle et al 1992). Parahippocampal activation during auditory hallucinations may thus represent a neural (but not necessarily conscious) response to internal speech which the subject was unaware he had generated.

The prominent involvement of the right hemisphere during auditory hallucinations may seem surprising given that the patients were perceiving speech, but is consistent with data from previous neuroimaging (Woodruff et al 1995, Dierks et al 1999) and EEG studies (Line et al 1998) of auditory hallucinations, and with the greater right fronto-temporal activation when subjects imagine another person's speech, as opposed to their own (Shergill et al 2001). Moreover, as auditory hallucinations in schizophrenia are typically derogatory and hostile in tone, the prominent engagement of right hemispheric areas might reflect processing of the prosody (George et al 1996) and inference of what is being said (Bottini et al 1994), as well as an emotional response to its content (Canli et al 1998). Another possibility is that the right-sided activation is related to abnormal lateralisation of language, as evident from some of the structural MRI data (Maher et al. 1998), although more recent evidence does not support this finding (Shapleske et al 2001).

A methodological limitation of this study is a lack of knowledge about the nature of resting (in this case, non-hallucinating) brain activity in the patients: it is possible that this is different from that in other non-hallucinating schizophrenic patients and normal individuals. This issue could be explicitly investigated using the sampling technique in future studies. A further limitation of the sampling approach is that it cannot provide precise information about the timing of hallucinations, such as the point of onset or length of the preceding hallucinatory experience, and is reliant on the accuracy of self-report. Moreover, it is difficult to find large numbers of patients that are suitable for this type of study; most patients find entering a MRI scanner while experiencing hallucinations to be an aversive experience and few patients have the frequent but intermittent pattern of hallucinations necessary for this type of study and the relatively small sample size could serve to reduce the validity of the findings. However, we attempted to overcome the limitations of small numbers by firstly, using fMRI to acquire a relatively large number of images in each subject and secondly, using both the sampling and button press technique within the same scanning session provided an internal control condition. The broad similarity between the findings obtained with two fundamentally different methods provides a construct validation of the results.

In conclusion, this study suggests that auditory hallucinations involve a distributed network of cortical and subcortical areas. The engagement of both cortical and subcortical elements of the auditory pathway during hallucinations makes it easier to appreciate why patients often describe these experiences as indistinguishable from "real" auditory perceptions. Defining the brain areas that mediate auditory hallucinations facilitates our understanding of their basis in cognitive, as well as biological, terms and provides a scientific rationale for their treatment using recently developed psychological (Shergill et al 1998) and biological strategies (Hoffman et al 2000) which are currently undergoing clinical evaluation. Overall, the results are consistent with the notion that auditory hallucinations involve a distributed set of functionally related areas rather than arising via an epileptiform focus in auditory cortex (David et al 1994). The relationship of these areas to those involved in putatively related cognitive processes is examined in Chapters 4-7.

Chapter 4

Neural Correlates of Inner Speech and Auditory Verbal Imagery in Different Forms

Background

Auditory verbal imagery refers to the process of imagining speech. This can occur naturally, e.g. when attempting to recall what someone said, but can also be deliberate, e.g. when consciously recalling the sound of someone's voice. Auditory imagery has been relatively understudied in comparison with the burgeoning psychological and functional neuroimaging literature on visual imagery, and there are even less data on auditory verbal imagery. Functional neuroimaging studies using single photon emission computerised tomography (SPECT) indicate that imagining non-verbal sounds, such as the barking of a dog, is associated with activation in the right temporal cortex (Goldenberg et al 1991), and lesions in the right temporal cortex impair musical imagery (Zatorre and Halpern 1993). Psychological studies (Reisberg et al 1991, Smith et al 1995) suggest that the interaction between "inner" speech and the "inner ear" is crucial for effective auditory verbal imagery. The only neuroimaging study of auditory verbal imagery (AVI) to date used Positron Emission Tomography (PET) and found that imagining another person's speech, relative to generating inner speech in one's own voice, was associated with activation in the supplementary motor, anterior cingulate and precentral cortex, the fronto-parietal operculum, and the left superior temporal gyrus (McGuire et al 1996).

Auditory verbal imagery is of particular interest because of its putative relationship with auditory verbal hallucinations. Cognitive models propose that auditory verbal hallucinations (AH) are derived from inner speech that the patient has mis-identified as alien (Frith & Done 1989). Auditory verbal imagery bears some resemblance to an AH, in that the subject perceives the sound of another person's speech in the absence of an external stimulus. However, while normal inner speech seems to be experienced mainly in the first person (e.g. "I will ....."; Hulbert et al 1994), AH in schizophrenia are usually in the second or third person e.g. "You will..." or "He will..." (Nayani and David 1996). The reason for this apparent disparity between the grammatical forms of inner speech and AH is unclear. One way of approaching this issue is to examine the relationship between the neural correlates of AVI in the first, second and third person.

Inner speech and first person auditory verbal imagery are likely to differ from imagery in the second and third person because imagining another person's voice places greater demands on the generation and monitoring of inner speech (McGuire et al 1996). Furthermore, there may also be differential engagement of visuo-spatial imagery; first person imagery involves only the subject, second person involves a speaker addressing the subject, while third person imagery involves a speaker referring to the subject as if in conversation with a third person.

In this study, I examined the neural correlates of auditory verbal imagery in normal subjects using functional magnetic resonance imaging (fMRI); this permitted a more powerful and sophisticated design than was previously possible using PET. Subjects performed four tasks; a) The silent articulation of sentences, b) Imagining speech in their own voice (first person imagery), c) Imagining sentences spoken in another's voice, addressed to the subject (second person imagery) and d) Imagining sentences spoken by another about them (third person imagery).

I predicted that: -

1. All tasks would be associated with activation in the left inferior frontal gyrus/insula; corresponding to a common component of silent articulation (Paulesu et al 1993, McGuire et al 1996).
2. Auditory verbal imagery (in general) would be associated with activation in the lateral temporal cortex, corresponding to the monitoring of inner speech (McGuire et al 1996).
3. Second and third person imagery would be associated with more activation in the left frontal and temporal cortex than imagining one's own speech, as imagining "alien" speech places greater demands on the generation and monitoring of inner speech (McGuire et al 1996).
4. Second and third person imagery would also be associated with activation in the posterior parietal cortex, associated with the visuo-spatial imagery of the speaker in relation to another listener (Corbetta et al 1993, 1995).

Methods

Subjects

Eight male volunteers, right-handed according to Annett's (1970) scale, aged 26-37 years (mean age 33) participated in the study. They did not suffer from medical or psychiatric disorders and were not receiving medication, and had no family history of psychiatric disorder. Their mean IQ, estimated with the National Adult Reading Test (NART; Nelson 1991) was 114 (range 100-120). Potential subjects were assessed on their ability to perform the tasks (detailed below) outside the scanner. They rated their ability to perform each task on a visual analogue scale and were included if, after training, they consistently scored above 8/10 on this scale on all tasks. Subjects gave written informed consent to the study, which had been approved by the Maudsley hospital ethical committee.

Tasks performed during fMRI

All tasks required that subjects listened to single words presented every 3 seconds in the neutral voice that they had heard during training. The words consisted of nouns and adjectives which could readily complete a sentence of the form "I like .....", or "I like being....." . The words were matched for familiarity, frequency of occurrence and imageability across conditions. Each task comprised an "active" and a baseline condition. Before the baseline condition, subjects heard the prompt "now listen", while the "active" conditions were preceded by "imagine". Speech was presented via pneumatically driven headphones, incorporated within ear defenders, specifically designed for functional MRI (Quiet Muff 29 Earmuffs, Avotec, Jensen Beach, Fl, USA). These reduced unattenuated noise from our gradient switching frequency for EPI (1 kHz) from 109 dB to approximately 68 dB. Attenuated noise at the second, third and fourth harmonics (2 kHz, 3 kHz, 4 kHz) was approximately 44-56 dB. Subjects had their eyes closed during scanning.

Four "active" conditions were each compared with the same baseline condition. Each task involved 10 alternating 30-second blocks of each condition, lasting a total of five minutes. Task order was counterbalanced across subjects.

Baseline

Subjects were instructed to listen to each word carefully.

Inner Speech

On hearing each word, subjects were asked to silently articulate a sentence of the form "I like....", or "I like being...", ending in the presented word.

First Person Imagery

The instructions were identical to the inner speech condition, except that subjects had to imagine the sentence being spoken in their own voice.

Second Person Imagery

Subjects were asked to complete a sentence in the form "You like....", or "You like being...", ending in the presented word, and to imagine this spoken to them in the voice they had heard on the training tape.

Third Person Imagery

The instructions were identical to the second person imagery condition, except that the sentence was in the form "He likes....", or "He likes being...", as if spoken about the subject.

After completing each task, subjects rated their ability to perform it as instructed, using a visual analogue scale. They were also asked about their experience of the baseline task to ensure that no imagery had occurred during the baseline phase. In order to reduce potentially confounding effects of poor performance on activation, due to the distraction of being in the scanning environment, only data from subjects who provided ratings of greater than 5/10 on all tasks were analysed.

Image Acquisition

Gradient-echo echoplanar MR images were acquired using a 1.5 Tesla GE Signa System (General Electric, Milwaukee, WI, USA) fitted with Advanced NMR hardware and software (ANMR, Woburn, MA, USA) at the Maudsley Hospital, London. A quadrature birdcage head coil was used for RF transmission and reception. In each of 14 non-contiguous planes parallel to the inter-commissural (AC-PC) plane, 100 T2*-weighted MR images depicting BOLD contrast (Ogawa et al., 1990) were acquired with TE = 40ms, TR= 3000ms, in-plane resolution = 3.1 mm, slice thickness = 7mm, slice skip = 0.7mm. Head movement was limited by foam padding within the head coil and a

restraining band across the forehead. At the same session, a 43 slice, high-resolution inversion recovery echoplanar image of the whole brain was acquired in the AC-PC plane with TE = 73 ms, TI= 180 ms, TR = 16,000 ms, in-plane resolution = 1.5 mm, slice thickness = 3 mm.

Generic Brain Activation Mapping

Analysis was carried out as described in chapter 2. Generically activated voxels were coloured and superimposed on the grey scale Talairach template, to create generic brain activation maps (GBAMs) (Brammer et al., 1997). The timing of the signal increase relative to the input function was ascertained and activated voxels with signal maximum during the active task were coloured red; activated voxels with signal maximum during baseline task were coloured blue.

The GBAM's for the imagery tasks were combined, taking the mean activation over all 3 imagery conditions versus baseline, to identify the consistent correlates of auditory verbal imagery. To estimate the between-task differences in the power of the physiological response to the experimental tasks, the following repeated measures analysis of variance (ANOVA) model was fitted at each intracerebral voxel in standard space:

$$FPQ_{i,j} = \beta_0 + \beta_1 Task_j + e_{i,j}$$

Here $FPQ_{i,j}$ denotes standardised power at the $_i$th voxel in the $_j$th member of the group, : β_0 denotes the overall mean power, and $e_{i,j,}$ is a residual quantity. Task is a factor coding for task (is or 1st or 2nd or 3rd). The null hypothesis of zero between-group difference in mean power of response was tested by comparing the coefficient to its non-parametrically ascertained null distribution. To do this the elements of Task were randomly permuted 10 times at each voxel, taking account of the repeated measures nature of the data (Edgington, 1980), β_1 was estimated after each permutation, and these estimates were pooled over all intracerebral voxels to sample the permutation distribution of β_1. Critical values of a 2-tailed test of size p=0.01 were the 100.(p/2)th and 100.(1-p/2)th percentiles of this distribution (Bullmore et al 1996, 1999b; Edgington 1980). Note that this relatively lenient probability threshold was used only to test a restricted search volume comprising those voxels that were

generically activated by the task in one or both groups. Comparisons were made between: - a) inner speech and first person imagery (to examine the substrate of imagery), and b) first person imagery and combined second and third person imagery (to examine the correlates of "self" versus "alien" imagery).

Results

Auditory Verbal Imagery Ratings

Two individuals originally recruited for the study were unable to adequately perform the imagery tasks when inside the scanner, reporting that scanner noise made concentration difficult, and rating their performance on some tasks as less than 5/10. The data from these subjects was not analysed. The remaining six subjects reported that they were able to perform the tasks as instructed and scored above 5/10 on all tasks. They gave lower ratings for the tasks that involved imagining another persons voice, (second person imagery- mean score 7.0 [range 6.5-9.0] and third person imagery- mean score 6.5 [range 6.0-9.0]), than those that involved their own voice (inner speech- mean 9.0 [range 8.5-10.0] and first person imagery - mean 8.5 [range 8.0-9.5]); significantly different at $p<0.005$ ($t=5.6$, 95% confidence intervals 1.1 to 3.1) (Figure 4.1).

Imaging Data

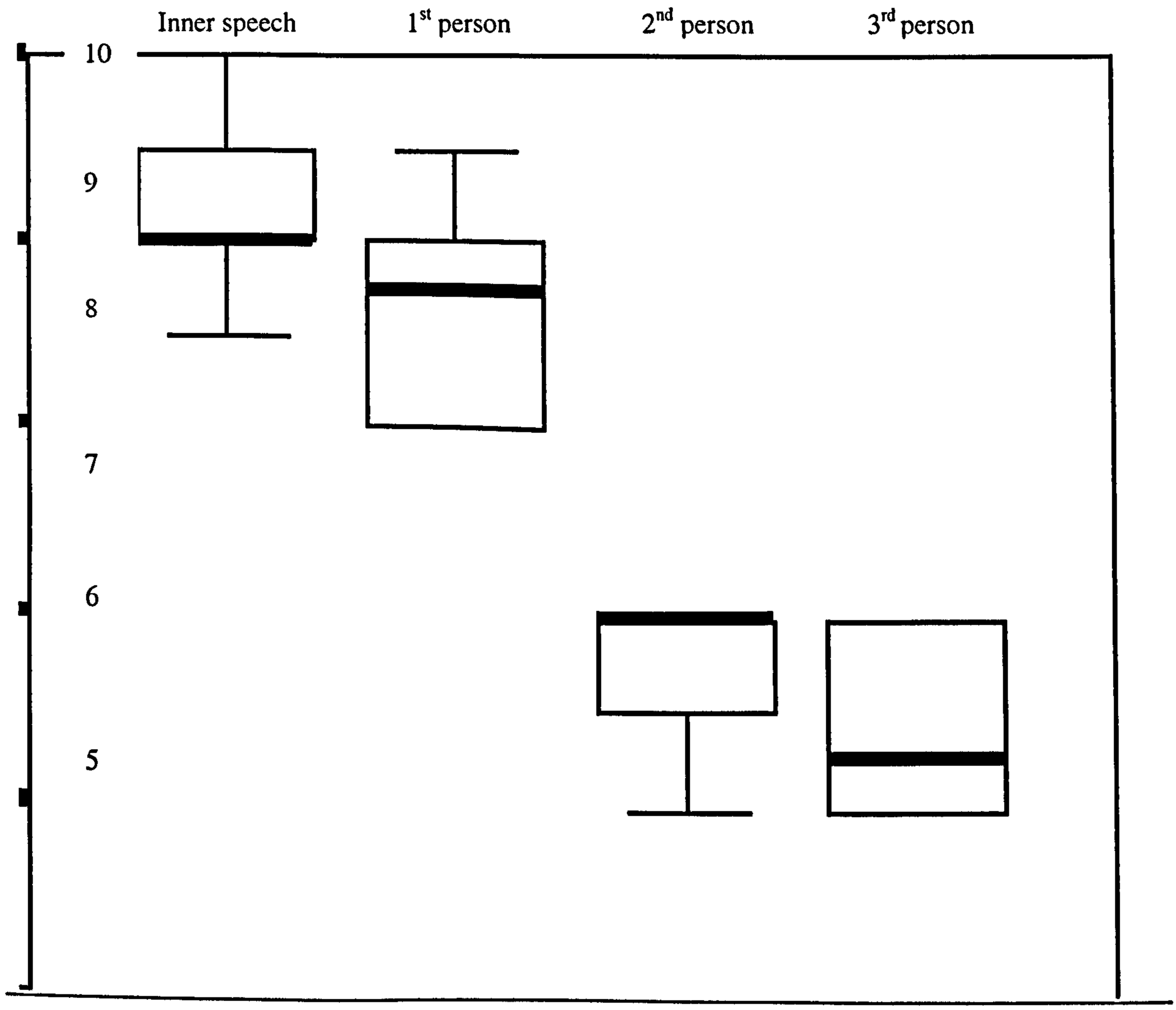
Inner Speech

Compared to baseline, the inner speech condition was associated with left-sided activation in the inferior frontal gyrus, insula, the junction of the superior temporal gyrus (STG) and inferior parietal lobule, and the superior parietal lobule (Figure 4.2). Activation was also evident in the supplementary motor area (SMA) and the right posterior cerebellar cortex. There were responses in phase with the baseline condition in the postcentral gyri, the medial prefrontal and parietal cortex and in the posterior cingulate gyrus (Table 4.1).

Imagining first person speech

Areas activated in phase with imagining one's own speech included the left insula, the precentral, postcentral and middle temporal gyri and the inferior parietal lobule (Figure 4.2). Activation was also evident in the SMA, posterior cerebellar cortex bilaterally and the right inferior frontal gyrus, inferior parietal lobule, fusiform gyrus and thalamus (Table 4.2). There were responses in phase with the baseline condition

Figure 4.1 Subjective ratings of auditory imagery tasks



The subjective ratings (scale 0-10), on the vertical axis, for each of the four conditions (on the horizontal axis); inner speech, first person, second person and third person. Boxplot displaying the mean value (bold line) with 95% confidence intervals (shaded area) and range (whiskers).

Figure 4.2 Activation during generation of inner speech, and auditory imagery in the first, second and third person

Areas activated during: (i) inner speech relative to baseline; (ii) first person imagery relative to baseline; (iii) second person imagery relative to baseline; and (iv) third person imagery relative to baseline. Activation maps were rendered onto a template, generated from the coregistered structural MRIs from all 6 subjects, and correspond to Talairach space. Selected axial slices are displayed parallel to the Anterior commissure-Posterior commissure plane and the left side of the figure represents the right side of the subjects and vice versa. Areas shown in red depict clusters significantly activated during the first condition, while blue depicts regions activated during the baseline condition.

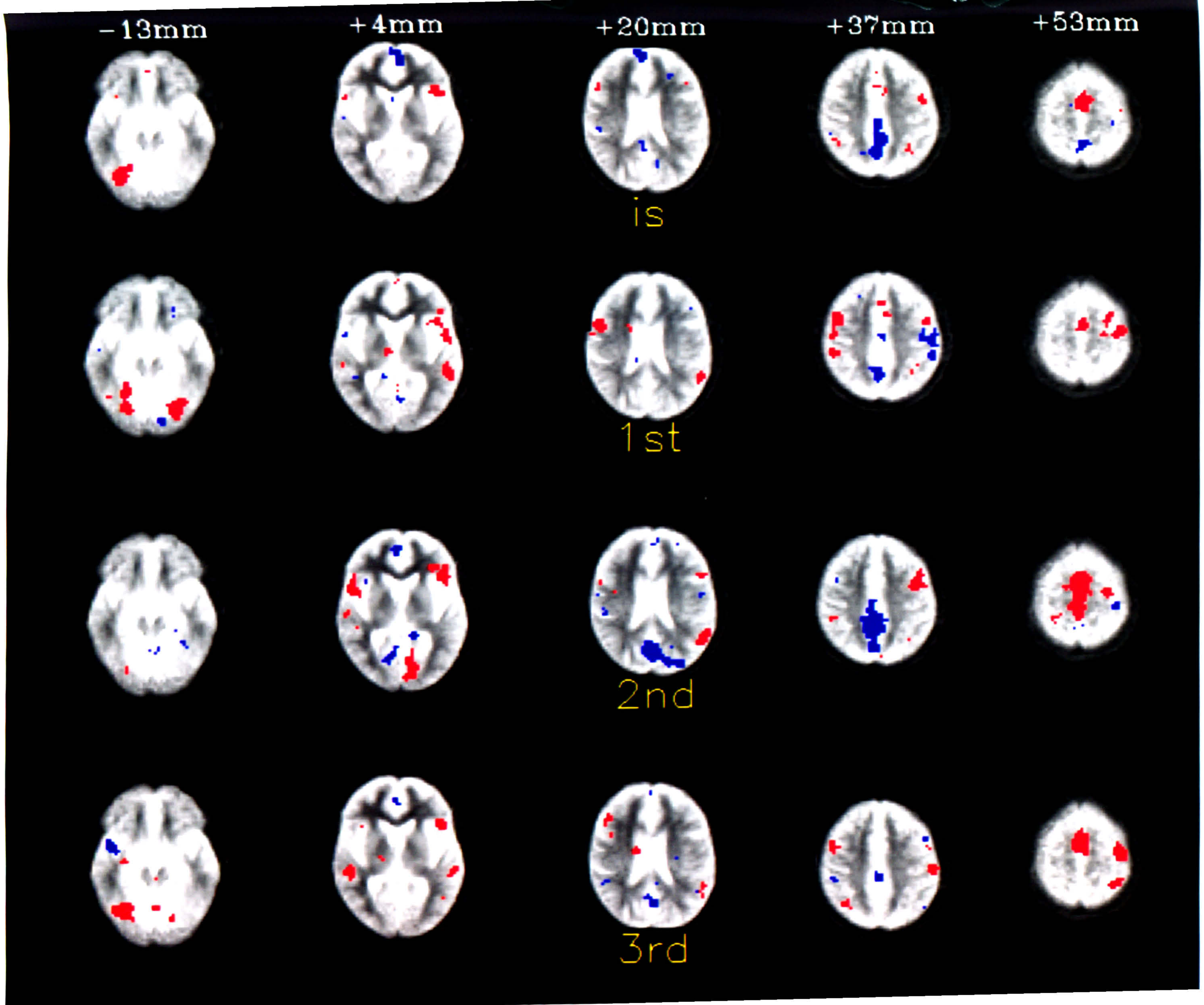

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Table 4.1 Main foci of activation inner speech task.

REGION	No. Voxels	X	Y	Z	MAX FPQ	P
Activation during INNER SPEECH						
L STG /Inf parietal cortex (BA 22/39)	13	-52	-53	26	2.4	0.000005
R. Posterior cerebellar cortex	29	26	-64	-18	2.2	0.000005
SMA(BA 6)	42	0	0	53	2.0	0.000015
L. Sup parietal lobule (BA 7)	13	-26	-53	42	2.0	0.000015
L. Inf frontal gyrus (BA 44) *	6	-46	11	26	1.9	0.000050
L. Insula	7	-38	14	4	1.7	0.000500
Activation during BASELINE						
Med frontal gyrus (BA 10)	24	0	56	4	2.2	0.000005
Post cingulate gyrus (BA 31)	32	0	-42	37	2.1	0.000005
Med parietal cortex (BA 7)	26	3	-56	37	2.1	0.000010
R Post central gyrus (BA 1,2,3)	6	52	-22	42	2.0	0.000020
L Postcentral gyrus (BA 3)	4	-49	-14	42	1.9	0.000030

Key

X,Y,Z	refer to the coordinates of maximal response in the atlas of Talairach and Tournoux (1988)		
No. Voxels	number of suprathreshold voxels in cluster focussed at this coordinate		
MAX FPQ	Maximal value of the Fundamental Power Quotient		
BA	Brodmann's Area		
L	left	R	right
INF	inferior	SUP	superior
STG	superior temporal gyrus	MTG	middle temporal gyrus
ANT	anterior	MED	medial
*	region of activation evident in the PET study of McGuire et al 1996		

Table 4.2 Main foci of activation, first person auditory verbal imagery.

REGION	NO. Voxels	X	Y	Z	MAX FPQ	P
Activation during IMAGINING OWN SPEECH						
SMA	21	3	-3	53	2.3	0.000005
L. Inf parietal lobule (BA 40)	16	-49	-42	26	2.3	0.000005
R. Posterior cerebellar cortex	10	26	-69	-13	2.3	0.000005
R. Fusiform gyrus (BA 37)	22	29	-58	-7	2.2	0.000005
L. Precentral gyrus (BA 4)	19	-43	-11	48	2.2	0.000005
L. Posterior cerebellar cortex	27	-23	-69	-13	2.1	0.000020
L. Postcentral gyrus (BA 1,2,3)	19	-43	-19	42	2.1	0.000015
L. Mid temporal gyrus (BA 21)	11	-52	-39	4	2.1	0.000005
R. Inf. Parietal lobule (BA 40)	16	49	-31	42	2.0	0.000050
R. Thalamus	14	12	-17	4	1.9	0.000075
R. Inf frontal gyrus (BA 44)	10	49	3	20	1.8	0.000250
L. Insula	6	-38	14	4	1.8	0.000250
Activation during BASELINE						
R Mid frontal gyrus (BA 9)	7	49	8	42	2.3	0.000005
Medial frontal gyrus (BA 10)	17	3	53	9	2.1	0.000025
Post cingulate gyrus/med parietal cortex (BA 31/7)	13	6	-53	37	2.1	0.000005
Post cingulate gyrus (BA 31)	12	3	-33	31	2.1	0.000005
L lingual gyrus (BA 18)	7	-12	-83	-13	2.1	0.000015
Post cingulate gyrus (BA 30)	20	3	-50	9	2.0	0.000050
R Hippocampus	11	23	-36	-2	2.0	0.000060

in the left lingual gyrus, the posterior cingulate/medial parietal cortex, the medial frontal gyrus and in the right middle frontal gyrus and hippocampus.

Imagining second person speech

Regions activated in phase with imagining speech in the second person included the left inferior frontal, middle frontal and precentral gyri, the area around the junction of the left STG/inferior parietal lobule and the left posterior cerebellar cortex (Figure 4.2). There was extensive activation of the SMA and responses in the right inferior frontal and superior temporal gyri. Responses in phase with the baseline condition were evident in the left cuneus and cerebellar vermis, the anterior cingulate gyrus, the area around the junction of the posterior cingulate gyrus and paracentral lobule, and in the medial parietal cortex (Table 4.3).

Imagining third person speech

Imagining speech in the third person was associated with left sided activation in the insula, pre- and postcentral gyri, STG and the inferior parietal lobule (Figure 4.2). Further responses were evident in the SMA, the area around the junction of the right inferior and middle frontal gyri, the right STG and the right posterior cerebellar cortex. Responses in phase with the baseline condition were apparent in the anterior and posterior cingulate gyri, and around the junction of the posterior cingulate gyrus and medial parietal cortex (Table 4.4).

Auditory Verbal Imagery (first, second and third person imagery combined)

Activation in phase with the combined imagery conditions was evident in the left inferior frontal and precentral gyri, and around the junction of the left STG with the inferior parietal lobule (Figure 4.3). Midline activation was evident in the SMA, and there were right-sided responses in the inferior frontal, precentral and superior temporal gyri, the inferior parietal lobule and the posterior cerebellar cortex. Responses in phase with the baseline task were evident in the medial prefrontal cortex, around the junction of the posterior cingulate gyrus and in the medial parietal cortex, and the right inferior parietal lobule (Table 4.5).

Table 4.3 Main foci of activation, second person auditory verbal imagery.

REGION	No. Voxels	X	Y	Z	MAX FPQ	P
Activation during SECOND PERSON SPEECH						
SMA (BA 6)*	169	3	-3	48	3.0	0.000005
L. STG/ Inf parietal lobule (BA 22/40)*	34	-52	-44	26	2.3	0.000005
L. Middle frontal gyrus (BA 9)	17	-43	11	31	2.1	0.000005
L. Precentral gyrus (BA 4)*	17	-43	-8	48	2.1	0.000005
L. Cuneus (BA 17)	14	-6	-72	9	2.0	0.000005
R. Inf frontal gyrus (BA 44)*	8	52	8	26	2.0	0.000005
L. Inf frontal gyrus (BA 45)*	12	-38	19	4	1.9	0.000025
L. Posterior cerebellar cortex	3	-9	-72	-7	1.8	0.000005
R. Sup temporal gyrus (BA 22)	2	46	-25	9	1.6	0.000150
Activation during BASELINE						
Med parietal cortex (BA 7)	33	0	-61	42	2.8	0.000005
Ant cingulate gyrus (BA 32)	28	9	42	9	2.3	0.000005
Post cingulate gyrus /paracentral lobule (BA 31/5)	54	6	-31	42	2.2	0.000005
	30	0	-42	37	2.1	0.000005
L cuneus (BA 19)	20	-26	-78	20	2.0	0.000005
L cerebellar vermis	8	-9	-75	-18	2.0	0.000005

Table 4.4 Main foci of activation, third person auditory verbal imagery.

REGION	No. Voxels	X	Y	Z	MAX FPQ	P
Activation during THIRD PERSON IMAGERY						
L Precentral gyrus (BA 4)	60	-40	-14	53	2.5	0.000005
SMA (BA 6)	46	3	-3	53	2.4	0.000005
L Postcentral gyrus (BA 1,2,3)	23	-52	-19	31	2.3	0.000005
R STG (BA 22)	28	49	-36	9	2.1	0.000010
R Posterior cerebellar cortex	24	32	-64	-13	2.1	0.000005
L Inf parietal lobule (BA 40)	18	-52	-44	26	2.1	0.000005
L. STG (BA 42)	17	-58	-31	9	2.1	0.000015
L Insula	9	-40	17	4	2.1	0.000010
R. Precentral gyrus/ Inf frontal gyrus (BA 6/44)	19	55	6	31	2.0	0.000075
R STG (BA 38)	8	46	3	-13	1.9	0.000175
Activation during BASELINE						
Posterior cingulate gyrus/ medial parietal cortex (BA 31/7)	17	-3	-67	26	2.1	0.000015
Rostral ant cingulate cortex (BA 32)	12	3	44	15	2.1	0.000020
Post cingulate gyrus (BA 23)	12	3	-42	26	2.0	0.000075

Figure 4.3 Activation during the generation of auditory imagery

Areas activated during auditory verbal imagery (first, second and third person imagery combined, relative to baseline). Activation maps were rendered onto a template, generated from the coregistered structural MRIs from all 6 subjects, and correspond to Talairach space. Selected axial slices are displayed parallel to the Anterior commisure-Posterior commisure plane and the left side of the figure represents the right side of the subjects and vice versa. Areas shown in red depict clusters significantly activated during the first condition, while blue depicts regions activated during the baseline condition.

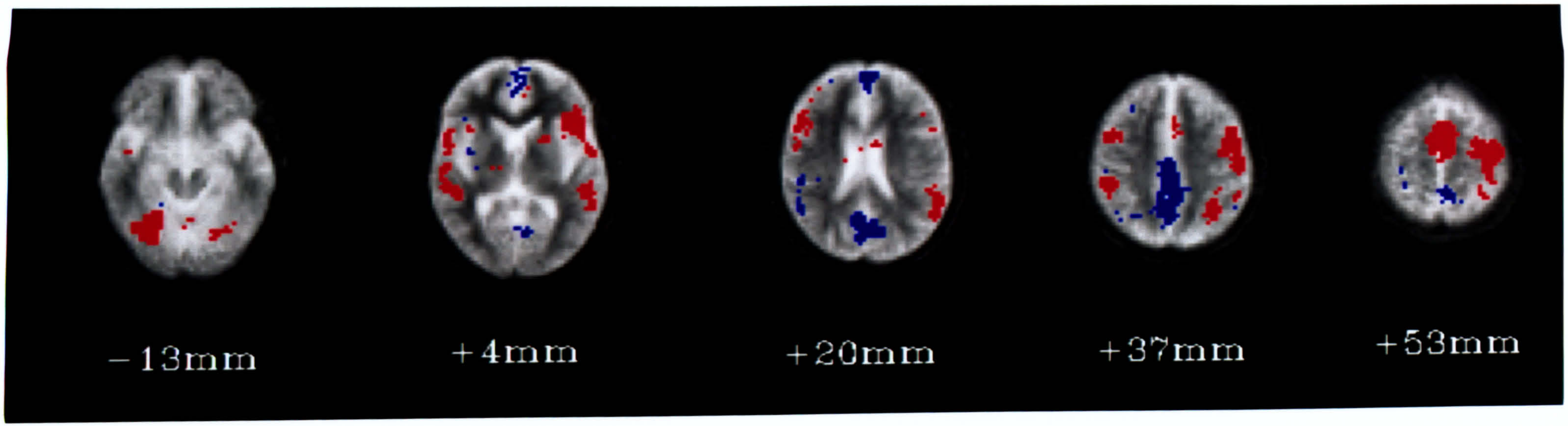
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Table 4.5. Main foci of activation, during combined imagining speech .

REGION	No. Voxels	X	Y	Z	MAX FPQ	P
Activation during combined IMAGINING SPEECH						
SMA (BA 6)	87	3	-3	53	2.5	0.000005
L STG/inf parietal lobule (BA 22/40)	36	-49	-42	26	2.3	0.000005
L Inf frontal gyrus (BA 45)	14	-43	17	4	2.1	0.000010
L Precentral gyrus (BA 4)	41	-40	-8	48	2.0	0.000005
R. Inf frontal gyrus (BA 44)	20	52	8	26	1.7	0.000005
R Cerebellar cortex	18	26	-58	-13	1.7	0.000005
R STG (BA 22)	15	46	-36	4	1.7	0.000005
L Precentral gyrus (BA 6)	14	-40	-3	37	1.7	0.000005
L. Inferior parietal lobule (BA 40)	12	-38	-39	48	1.7	0.000005
R Inf parietal lobule (BA 40)	11	46	-31	37	1.6	0.000020
R Precentral gyrus (BA 6)	8	43	3	37	1.6	0.000010
Activation during BASELINE						
R Inf parietal lobule (BA 40)	15	58	-28	26	1.8	0.000005
Medial frontal lobe (BA 10)	26	6	50	-2	1.8	0.000005
Post cingulate gyrus (BA 23)	31	3	-33	42	1.8	0.000005
Posterior cingulate gyrus/med parietal cortex (BA 31/7)	52	0	-64	20	1.7	0.000005

Differences between tasks

Only differences significant at $p<0.005$ are reported.

First person imagery versus inner speech

There was a greater response during imagining one's own voice, relative to inner speech, in the left insula, precentral gyrus and lingual gyrus and bilaterally in the middle temporal gyri and posterior cerebellar cortex. Right-sided changes were evident in the middle frontal gyrus, inferior parietal lobule, fusiform gyrus, the hippocampus and the thalamus. During the inner speech condition there was a greater response in the SMA, during the active task, and in the medial frontal gyrus, anterior and posterior cingulate gyri and the medial parietal lobule in phase with the baseline condition in the frontal pole, right middle frontal gyrus, left lingual and posterior cingulate gyri (Table 4.6).

Second and third person imagery combined versus first person imagery

Imagery of another's (second and third person imagery combined) voice was associated with greater activation in the SMA, the left precentral and middle temporal gyri and inferior parietal lobule, and right superior temporal gyrus and posterior cerebellar cortex (Figure 4.4). Second and third person imagery combined was also associated with greater responses in the medial parietal lobule and posterior cingulate gyrus during the baseline condition (Table 4.7).

Table 4.6

A) **Imagining own voice** versus inner speech

REGION	No. Voxels	X	Y	Z	Diff in Max FPQ	P<
Activation greater during imagining own voice						
L Precentral gyrus (BA 4)	20	-40	-8	48	0.7	0.000005
L Posterior cerebellar cortex	19	-26	-67	-13	0.7	0.000005
R Fusiform gyrus (BA 37)	16	26	-56	-7	0.6	0.000005
R Inferior parietal lobule (BA40)	4	49	-31	42	0.6	0.000005
R MTG (BA 21)	2	58	-17	-7	0.6	0.000005
R Thalamus (dm n.)	12	6	-11	9	0.5	0.000005
R Hippocampus	8	23	-33	-2	0.5	0.000005
L Lingual gyrus (BA 18)	7	-14	-81	-13	0.5	0.000005
R Middle frontal gyrus (BA 9)	7	52	8	37	0.5	0.000005
L Insula	5	-49	6	9	0.5	0.000005
R Posterior cerebellar cortex	5	20	-69	-13	0.5	0.000005
R Middle frontal gyrus (BA 10)	4	-40	42	-2	0.5	0.000005
L MTG (BA 21)	3	-52	-39	4	0.5	0.000005
Activation greater during inner speech (* in phase with baseline)						
SMA (BA 6)	*11*	*0*	*6*	*53*	*0.8*	*0.005*
*Posterior cingulate gyrus (BA 31)**	*56*	*-3*	*-42*	*37*	*1.5*	*0.00005*
*Medial frontal gyrus (BA 10)**	*12*	*-3*	*53*	*4*	*1.0*	*0.001*
*Medial parietal cortex (BA 7)**	*12*	*3*	*-56*	*31*	*0.8*	*0.005*
Ant cingulate gyrus (BA 32)*	*12*	*6*	*28*	*31*	*0.7*	*0.001*

Figure 4.4 Activation during auditory imagery of an alien voice relative to one's own.

Areas activated during combined second and third person imagery relative to first person. Selected axial slices are displayed parallel to the Anterior commisure-Posterior commisure plane and the left side of the figure represents the right side of the subjects and vice versa. Areas shown in red depict clusters significantly activated during imagery of another's voice.

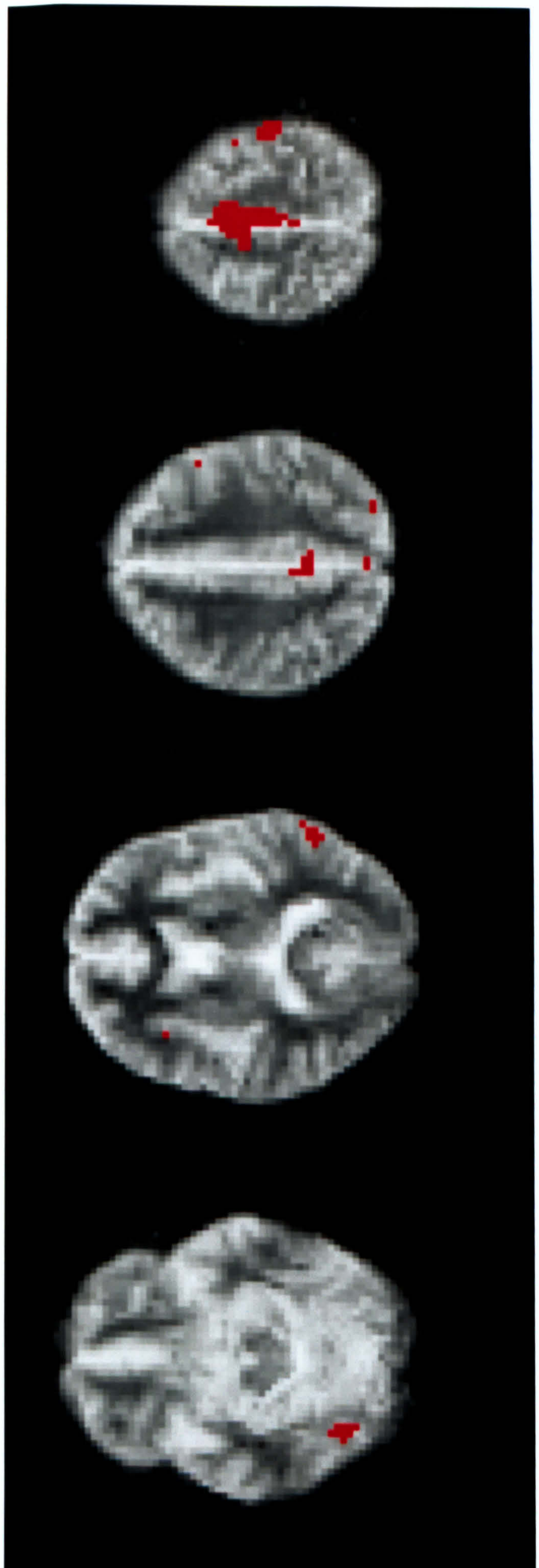


Table 4.7 **Combined second and third person imagery** versus first person imagery
(Activation greater during second and third person imagery)

REGION	No. Voxels	X	Y	Z	MAX β_1	P
SMA (BA 6)	73	3	11	53	0.5	0.000005
L Precentral gyrus (BA 4)	17	-40	-11	53	0.5	0.000005
R Posterior cerebellar cortex	9	35	-58	-13	0.5	0.000005
L MTG (BA 21)	7	-58	-44	9	0.5	0.000005
L Inf parietal lobule (BA 40)	7	-55	-36	26	0.5	0.000005
R STG (BA 22)	4	49	-25	4	0.5	0.000005
Medial parietal lobule(BA 7)*	9	-3	-58	42	0.7	0.000005
Post cingulate gyrus (BA 31)*	16	6	-33	37	0.6	0.000005

KEY

* GREATER ACTIVATION IN PHASE WITH BASELINE/ ("DECREASE") DURING THE ACTIVE CONDITION)

Discussion

Methodology

The aim of this study was to use fMRI to identify the neural correlates of inner speech and different forms of auditory verbal imagery. The inner speech and imagery tasks required subjects to generate and silently articulate/imagine sentences from cue words. The baseline condition (listening to the cue words) was designed to eliminate activation related to processing the cue, isolating responses specific to inner speech and auditory verbal imagery. The use of a stereotyped sentence prevented variation in the form of sentence construction beyond that specified by the task instructions.

Although all the original subjects were able to perform the tasks when outside the scanner (n=8), two proved unable to do so once lying inside it; their fMRI data was therefore not analysed. The remaining subjects (n=6) reported that the scanner noise (which was reduced to circa 60db by ear defenders) was occasionally a distraction but did not interfere with task execution. Although scanner noise can also influence the BOLD response in lateral temporal cortex (Bandettini et al 1998; Amaro et al 1999) significant, task-related, temporal cortical responses were still evident in this study, presumably because confounding effects of background noise were reduced by its constancy across conditions. Previous fMRI studies using the same MR scanner have also detected temporal cortical activation both in response to external speech (Woodruff et al 1997) and during tasks engaging covert verbal processing (Calvert et al 1997). Ideally, functional imaging studies of cognitive tasks should involve the measurement of behavioural performance "on-line", to assess how well subjects are carrying them out during scanning. However, auditory verbal imagery is a subjective phenomenon, and as such is not easily amenable to objective monitoring of performance. We thus sought to minimise the influence of variation in performance by training subjects on the tasks prior to scanning, obtaining ratings of their performance immediately after each task, and excluding those who reported marked difficulties with task execution.

Verbal generation and silent articulation

As predicted, the inner speech condition, that entailed the silent generation and articulation of speech, was associated with activation in the left inferior frontal cortex/insula. However, there was also activation in several regions that were not activated in the only previous PET study of auditory verbal imagery (McGuire et al

1996), such as the SMA, the left superior temporal/inferior parietal region, and the right posterior cerebellar cortex. This probably reflects the greater number of images acquired duringthe present study, which, because it employed fMRI, involved 400 images per subject as opposed to 12. While the inner speech condition involved semantic and grammatical processing that could have contributed to this pattern of activation, the use of a stereotyped sentence stem meant that the main demands were on covert generation/articulation and verbal working memory. Moreover, similar areas have previously been activated with other tasks that have engaged verbal working memory (Paulesu et al 1993) and silent articulation implicitly (Warburton et al 1996, Curtis et al 1998). The role of the right cerebellum in language and verbal working memory tasks has become more apparent with the increased use of functional neuroimaging, reviewed by Desmond and Fiez (1998); they suggest that the cerebellum displays activation both during cognitive manipulations requiring verbal working memory and those involving articulatory rehearsal. The same set of regions were also engaged during first, second and third person imagery, consistent with the notion that inner speech and auditory verbal imagery share a common component of verbal working memory and covert generation/articulation (Smith et al 1995, McGuire et al 1996).

Auditory verbal imagery

The auditory verbal imagery tasks probably placed greater demands on both covert generation and articulation and auditory attentional engagement than the inner speech task, because the subject had to reproduce an internal representation of speech with a particular sound (McGuire et al 1996). This would be consistent with our subjects rating the imagery tasks as subjectively more difficult than the inner speech task. Imagining speech is thought to entail retrieval of the voice to be imagined from memory and the internal reproduction and "inspection" of the auditory image (Reisberg et al 1991). Auditory verbal imagery in general, as indexed by the three imagery tasks combined, was associated with activation in the set of areas engaged during the inner speech task (left inferior frontal and parietal cortex and SMA), plus the left precentral and superior temporal gyri, and the right homologues of all these areas. Similar regions were activated, albeit less extensively, in the comparison between first person imagery and inner speech. We predicted the lateral temporal activation because this region is implicated in verbal monitoring, which is greater during auditory verbal imagery than inner speech (McGuire et al 1996; Wise et al 1991, Zatorre et al 1991, Zatorre &

Halpern 1993); while the engagement of the left inferior frontal gyrus/insula and precentral cortex during auditory verbal imagery was predicted because imagining speech places increased demands on silent articulation (McGuire et al 1996, Paulesu 1993, Price et al 1996).

The additional engagement of the right-sided homologues of the above areas suggests that they may play a role in retrieving and processing the prosody of the imagined speech, as they are activated when comparing melodies with matched non-melodic sequences, making pitch judgments on syllables (Zatorre et al 1992, Zatorre and Sampson 1991), assessing emotional prosody in spoken sentences (George et al 1996) and implicated in imagery of familiar tunes (Halpern et al 1999). The latter PET study of musical imagery also suggested that right frontal lobe activation was associated with retrieval from musical semantic memory, and confirmed the involvement of the SMA in image generation, proposing that it may be related to motor code in this process. These regions have also been associated with deficits in processing verbal prosody in lesion studies (Ross and Mesulam 1979, Pell 1998). However, an alternative, more general, explanation could be that increased task demands led to the recruitment of contralateral homologous regions, as evident in a recent fMRI study of mental rotation (Carpenter et al. 1999).

Imagining alien speech

The combined second and third person imagery, relative to first person imagery, was associated with activation in the left premotor, middle temporal and inferior parietal cortex, and in the SMA. The greater engagement of the premotor, inferior parietal and temporal cortex are consistent with the notion that imagining another's voice places more demands on covert articulation, engagement of auditory attention and on verbal monitoring, than imagining one's own (McGuire et al 1996).

There was no evidence to support the hypothesis of greater activation of cortical visuo-spatial areas during imagery of "alien" auditory imagery. The most likely reason for this failure is that task did not require subjects to evoke any visual imagery during these tasks.

Baseline Responses

Although there were differences in the extent to which they were engaged, the medial parietal and posterior cingulate cortex showed responses during the baseline of all the tasks. These changes may reflect a net shift of attention from visuospatial to language processing during the active condition such that resources are diverted away from areas irrelevant to the active task (McGuire et al 1996). Analogous changes, in the opposite direction, have been reported in the auditory cortex, during visual paradigms (Haxby et al 1994). A similar mechanism may account for the baseline responses we observed in the medial frontal cortex, as increased baseline activity in this region has also been noted during auditory verbal memory tasks (Grasby et al 1994).

Auditory Verbal Hallucinations

The areas engaged during inner speech and auditory verbal imagery in this study, particularly the inferior frontal/insular, lateral temporal and inferior parietal cortex, are similar to those identified in functional imaging studies of auditory verbal hallucinations (Chapter 3, McGuire et al 1993, 1996, Silbersweig et al 1995). This is consistent with the notion that verbal hallucinations are derived from a lack of awareness of the subject's normal inner speech (Frith 1992). However, patients with hallucinations are not usually conscious of generating the experience, whereas when volunteers imagine other people's speech they have no difficulty in recognising this as self-generated. In the present study, both the SMA and cerebellum were strongly activated during the inner speech and auditory verbal imagery tasks, particularly when subjects imagined "alien" speech, but appear to be relatively weakly engaged during auditory verbal hallucinations (Chapter 3, Silbersweig et al 1995, Dierks et al 1999). The SMA is thought to be the source of the Bereitschaft potential, which precedes the awareness of willed action (Deeke et al 1969, Deeke 1987), and lesions in this region are associated with the alien limb syndrome, in which the patient seems to lose awareness that his movements are self generated (Gasquoine 1993). Similarly, both lesion and neuroimaging studies suggest that the cerebellum normally acts as a "comparator" in both motor (Blakemore et al 1998) and verbal tasks (Desmond et al 1997), comparing intended with actual performance and modulating cerebral cortical activity appropriately (Andreasen et al 1998). These observations suggest activation in the SMA or the cerebellum may be a correlate of the subject being aware that an auditory verbal percept is self-generated. Conversely, the paucity of SMA and

cerebellar activation during auditory hallucinations might be related to a loss of this awareness. This is consistent with a case report of a patient with right lateral cerebellar damage, which resulted in an inability to correct verbal errors, of which the patient was often unaware (Fiez et al 1992).

While auditory imagery engages verbal self-monitoring, it may also increases demands on both phonological and semantic processing, relative to inner speech. The activation discussed above could thus be related to the latter aspects of the task rather than its monitoring component. In order to examine this issue, I carried out a study using another task, which was designed to engage verbal self-monitoring but place minimal demands on semantic and phonological processing. This study is described in Chapter 5.

Chapter 5

Neural Correlates of Verbal Self-monitoring

Background

Electrophysiological recordings in non-human primates (Müller-Preuss and Ploog 1981) and man (Creutzfeldt 1989) indicate that neuronal activity in the temporal cortex is powerfully modulated by vocalisation. This modulation can precede articulation and may be mediated by the direct anatomical connections that link areas that generate and perceive speech, in the frontal and temporal cortex respectively, (Pandya and Yeterian 1985). Similarly, some Positron Emission Tomography (PET) studies have indicated that when subjects generate words, the left dorsolateral prefrontal cortex (DLPFC) is activated while the temporal cortex is de-activated bilaterally (Frith et al 1995; Friston et al 1991). These studies suggest that output from regions involved in verbal generation may modulate activation in areas involved in speech perception, perhaps in order to inform them that impending verbal stimuli are self-generated (Chapter 1; Frith and Done 1989).

Most of the neuroimaging evidence for modulation of temporal activation during verbal generation is derived from studies of verbal fluency and auditory imagery (as in chapter 4). In both tasks, as well as articulation, generating a word or sentence in response to a cue involves phonological and semantic processing, processes that could also account for changes in frontal and temporal activation (Poldrack et al 1999; Wise et al 1999; Burton 2000). In the present study, I used functional magnetic resonance imaging (fMRI) to assess the relationship between frontal and temporal activation during the generation of the same word at different rates, in order to minimise phonological and semantic processing. I studied covert as opposed to overt articulation, as this eliminated the possibility that changes in temporal activation with increasing verbal output were simply a function of increased auditory input, rather than cortico-cortical modulation. I was also interested in establishing whether fronto-temporal modulation occurred during the generation of inner speech, as the interaction between areas that generate and monitor inner speech is putatively defective in patients with auditory hallucinations (Chapter 1; Frith and Done 1989). Covert articulation during other paradigms has been associated with activation in the left inferior frontal gyrus and the superior temporal gyrus (Chapter 4, Paulesu et al 1993;

McGuire et al 1996), but the relationship between the responses in these areas was not examined.

I predicted that:

1. Increasing the rate of covert articulation would be associated with activation in both the left inferior frontal and the left superior temporal gyrus
2. There would be a positive correlation between the activation in these regions.

Methods

Subjects

Eight male volunteers (different from those in chapter 4), right-handed according to Annett's (1970) scale, aged 23-37 years (mean age 29, SD 5) participated in the study. They did not suffer from medical or psychiatric disorders, were not receiving medication, and had no family history of psychiatric disorder. Their mean IQ estimated with the National Adult Reading Test (Nelson 1991) was 115 (range 106-117, SD 5). Before inclusion, potential subjects were assessed on their ability to overtly repeat a word at the three rates (once every 1,2 or 4 seconds) to be used during scanning. They proceeded to scanning when they consistently achieved a 1:2:4 ratios in the number of repetitions, at the respective rates, over a minute. Subjects provided written informed consent, and the local hospital ethical committee approved the study.

Tasks performed during fMRI

<u>Fast v Slow Covert Articulation (Categorical comparison).</u>

Subjects covertly generated the word "rest" repeatedly at two self-paced rates (once every 1 or 4 seconds = 60 or 15 words per minute), without speaking. Their accuracy was checked by asking them to tap their finger at the two different rates both prior to and immediately after scanning. During scanning, the two conditions alternated in an ABAB design, with each condition lasting 30 seconds and 5 cycles of each condition in a 300-second run. The order of conditions was counterbalanced across subjects. The desired rate during each condition was indicated by a number visible throughout in the centre of a computer screen ("1" for 1 word every second and "4" for one word every 4 seconds.

Fast/Intermediate/Slow Covert Articulation (Parametric Task).

Subjects covertly generated the word "rest" repeatedly at three rates (once every 1, 2 or 4 seconds = 60, 30 and 15 words per minute) without articulating the word. Their accuracy was checked before and after the task, as described above. Each condition lasted 30 seconds and the desired rate was indicated by a number on a computer screen ("1", "2" or "4") as above. The order of conditions was pseudo randomised.

In order to reduce potentially confounding effects of poor performance on activation, only data from subjects who achieved a consistent timing ratio (on finger tapping) of 1:2:4 between the fast, intermediate and slow rate, immediately before and after scanning, were analysed.

Image Acquisition

Image acquisition is described in detail in chapters 2 and 5.

Image Analysis

Image analysis was performed on a SPARC Ultra 10 workstation (Sun Microsystems, Palo Alto, CA) using MATLAB (version 5.3, The Mathworks Inc, Natick, MA) and SPM99 software (Statistical Parametric Mapping, The Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm). All data sets were automatically realigned to the first image to correct for head movement, normalised using sinc interpolation and transformed into Talairach space. The transformed data set for each subject was smoothed with a Gaussian filter (Full width half maximum =8mm) to compensate for normal variation in anatomy across subjects. The time series were high pass (126 s) filtered to remove low frequency artifacts.

Statistical analysis was performed for each subject, and the stereotaxically normalised fMRI time series data from all the subjects pooled for group analysis. Analysis of the two-condition task (15 versus 60 words a minute) used a categorical design comparing activation evident during fast greater than slow rate of generation, and vice versa. Analysis of the three-condition task (15, 30 and 60 words/minute) used a parametric design to identify areas where activation was linearly correlated (positively and negatively) with the rate of covert articulation. Cluster level statistics corrected for multiple comparisons were thresholded at $p<0.05$.

Correlational analysis of time series data

In order to clarify the polarity of any fronto-temporal modulation (i.e. to determine whether it was positive or negative), we examined the BOLD response over time at the focus of maximal activation in six regions. These comprised the areas where we predicted modulation (the left inferior frontal and left superior temporal cortex), plus the four other most prominently activated regions. The fMRI time series, adjusted for motion correction and linear trends via a high pass filter, at the voxel showing peak response within each region was extracted for all subjects. The time series data were placed in an interregional correlation matrix to examine the functional connectivity in more detail.

Results

Behavioural data

All subjects were able to perform the task within the scanning environment and showed a consistent 1:2:4 timing ratio for the 3 conditions, both pre and post scanning. As a result, data from all subjects were included in the analysis.

Categorical comparison

Relative to covert generation at 15 words per minute, covert generation at 60 words per minute was associated with activation in foci in the dorsolateral and the orbital portions of the left inferior frontal gyrus, and in the anterior part of the left superior temporal gyrus. There was also a large area of activation centred on the right precentral gyrus, which included foci in the postcentral and superior temporal gyri, and further activation in the frontal pole (Figure 5.1; Table 5.1). The slower rate of generation was associated with activation in the supplementary motor area (SMA), the left precentral gyrus and the right inferior parietal lobule (Figure 5.2; Table 5.1).

Parametric analysis

The parametric analysis revealed that as the rate of generation increased, there was activation in the left inferior frontal gyrus, the left hippocampus and precuneus, and in the right precentral gyrus, and the posterior part of the right superior temporal gyrus (Table 5.2). Conversely, there was relatively decreased activation in the left precentral

and occipital gyri, the right inferior frontal and superior temporal gyri, and the right inferior parietal lobule and precuneus (Table 5.2).

Correlational analysis of time series data

There was a significant positive correlation between the BOLD response in the foci in the left inferior frontal and the left superior temporal gyri (Figure 5.3; Table 5.3). The results show the Pearson coefficient, although the results were still significant when Kendall's tau or Spearman's coefficient were computed. There were also negative correlations between the left inferior frontal signal and the responses in the left precentral and the right inferior parietal foci (Table 5.3). The BOLD responses in the SMA, the left precentral gyrus and the right inferior parietal lobule were significantly inter-correlated (Table 5.3).

Figure 5.1 Regions associated with faster rate of generation of inner speech (60 Vs 15 words per minute)

Areas shown in red/gold depict clusters significantly activated during the faster rate of covert articulation relative to slower rate. Group activation maps from all 8 subjects are displayed on a glass brain, and correspond to Talairach space. Axial slices are displayed parallel to the Anterior commissure-Posterior commissure plane, with the right side of the figure representing the right side of the subjects brain. Prominent activations are evident in the left inferior frontal and superior temporal gyri, the frontal pole and a large area on the right with foci in the superior temporal, precentral and postcentral gyri.

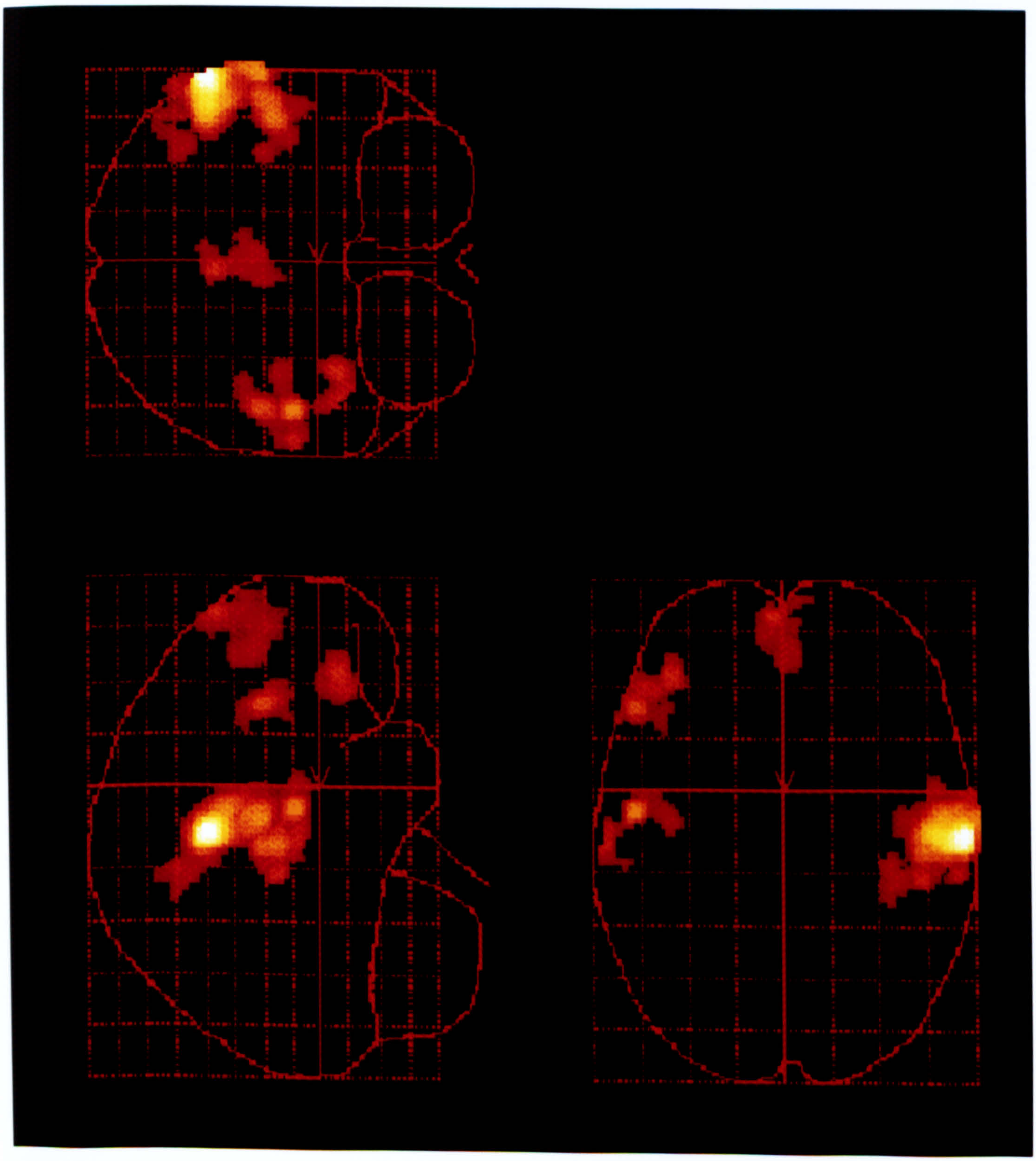


Figure 5.2 Regions associated with slower rate of generation of inner speech (15 Vs 60 words per minute)

Areas shown in red/gold depict clusters significantly activated during the slower rate of covert articulation relative to faster rate. Group activation maps from all 8 subjects are displayed on a glass brain, and correspond to Talairach space. Axial slices are displayed parallel to the Anterior commissure-Posterior commissure plane, with the right side of the figure representing the right side of the subjects brain. Prominent activations are evident in the SMA, the left precentral gyrus and the right inferior parietal lobule.

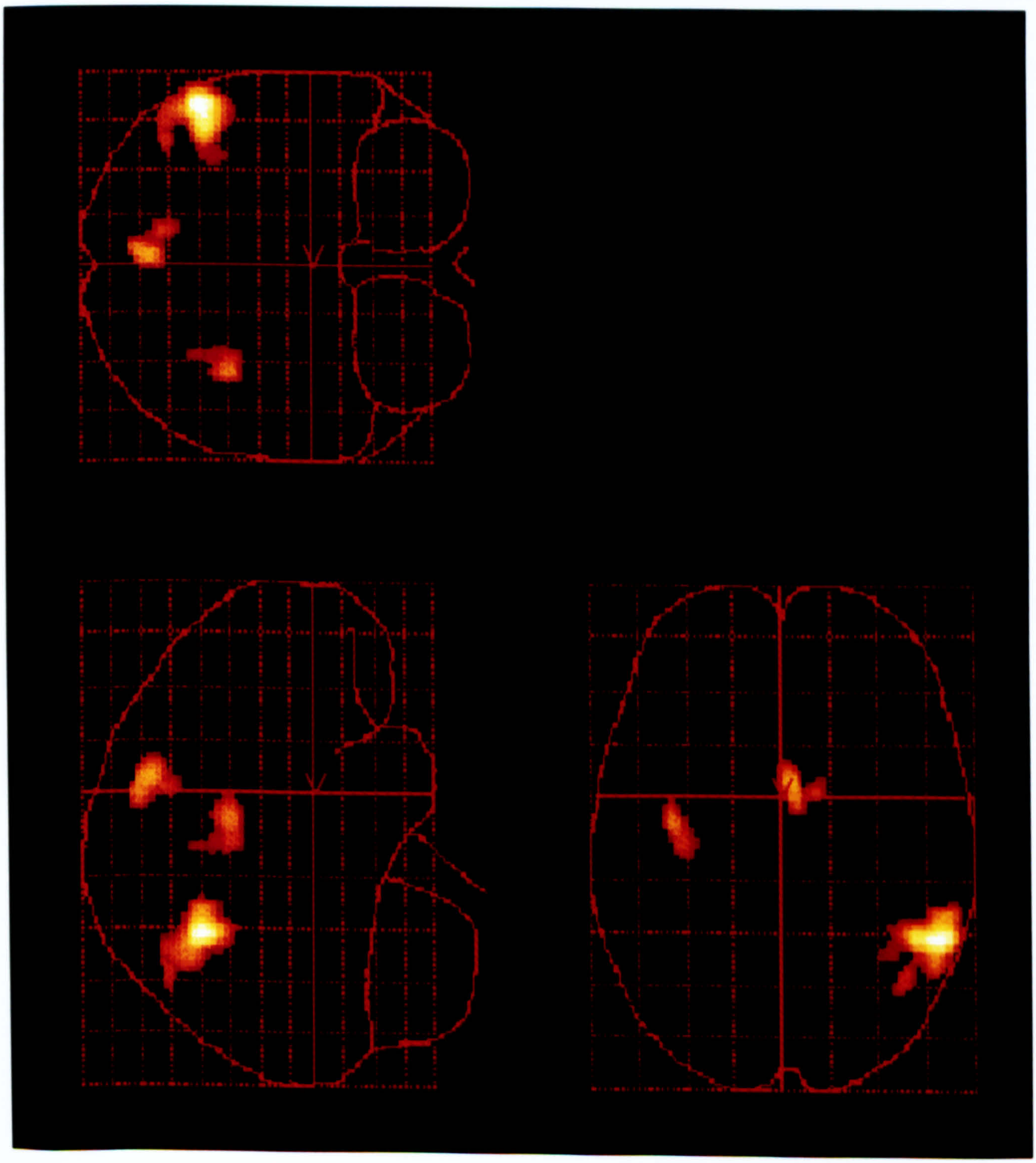


Table 5.1

Regions demonstrating significant activation during faster and slower rates (categorical analysis)

REGION	X	Y	Z	Cluster size (No. voxels)	P (cluster)
Greater activation at FASTER rate					
Left Inferior frontal gyrus (BA 45/46)	-52	30	20	154	0.008
(BA 47)	-38	40	-8	134	0.015
Left Superior temporal gyrus (BA 42)	-52	-8	8	239	0.001
Right Precentral gyrus (BA 6/4)	64	-16	40		
				1549	0.0001
Right Postcentral gyrus (BA 1,2,3)	66	-12	22		
Right Superior temporal gyrus (BA 42)	50	-20	16		
Frontal pole	-2	60	36	367	0.0001
Greater activation at SLOWER rate					
Right Inferior Parietal lobule (BA 40)	54	-48	40	541	0.0001
Supplementary motor area	4	6	58	143	0.01
Left Precentral gyrus (BA 4)	-38	-8	30	124	0.02

Table 5. 2

Regions demonstrating activation with increasing rate (parametric analysis) of generation

REGION	X	Y	Z	Cluster size (No. voxels)	P (cluster)
Greater activation with FASTER rate					
Left Inferior Frontal Gyrus (BA 45/46)	-54	32	22	145	0.01
Right Precentral gyrus (BA 6/4)	58	-4	42	280	0.0001
Right Superior temporal gyrus (BA 22)	66	-50	12	604	0.0001
Left Hippocampus	-28	-16	-8	183	0.003
Left Precuneus (BA 7)	-26	-82	42	114	0.03
Greater activation with SLOWER rate					
Right Inferior parietal lobule (BA 40)	58	-42	50	158	0.007
Left Precentral gyrus (BA 4)	-40	-10	50	123	0.02
Right Inferior frontal gyrus (BA 47)	50	28	-4	173	0.004
Right Superior temporal gyrus (BA 22)	58	-24	0	117	0.03
Right Precuneus (BA 7)	16	-82	48	327	0.0001
Left Middle occipital gyrus (BA 18)	-28	-74	12	136	0.01

Figure 5.3 Foci of activation demonstrating positive correlation with activation in the inferior frontal gyrus

Areas shown in red/gold depict clusters were significantly positively correlated with the left inferior frontal region (foci of maximum activation during the faster rate of covert articulation relative to slower rate). Group activation maps from all 8 subjects are displayed on a glass brain, and correspond to Talairach space. Axial slices are displayed parallel to the Anterior commissure-Posterior commissure plane, with the right side of the figure representing the right side of the subjects brain. Prominent activations were evident in the left inferior frontal and superior temporal gyri and the right postcentral gyrus.

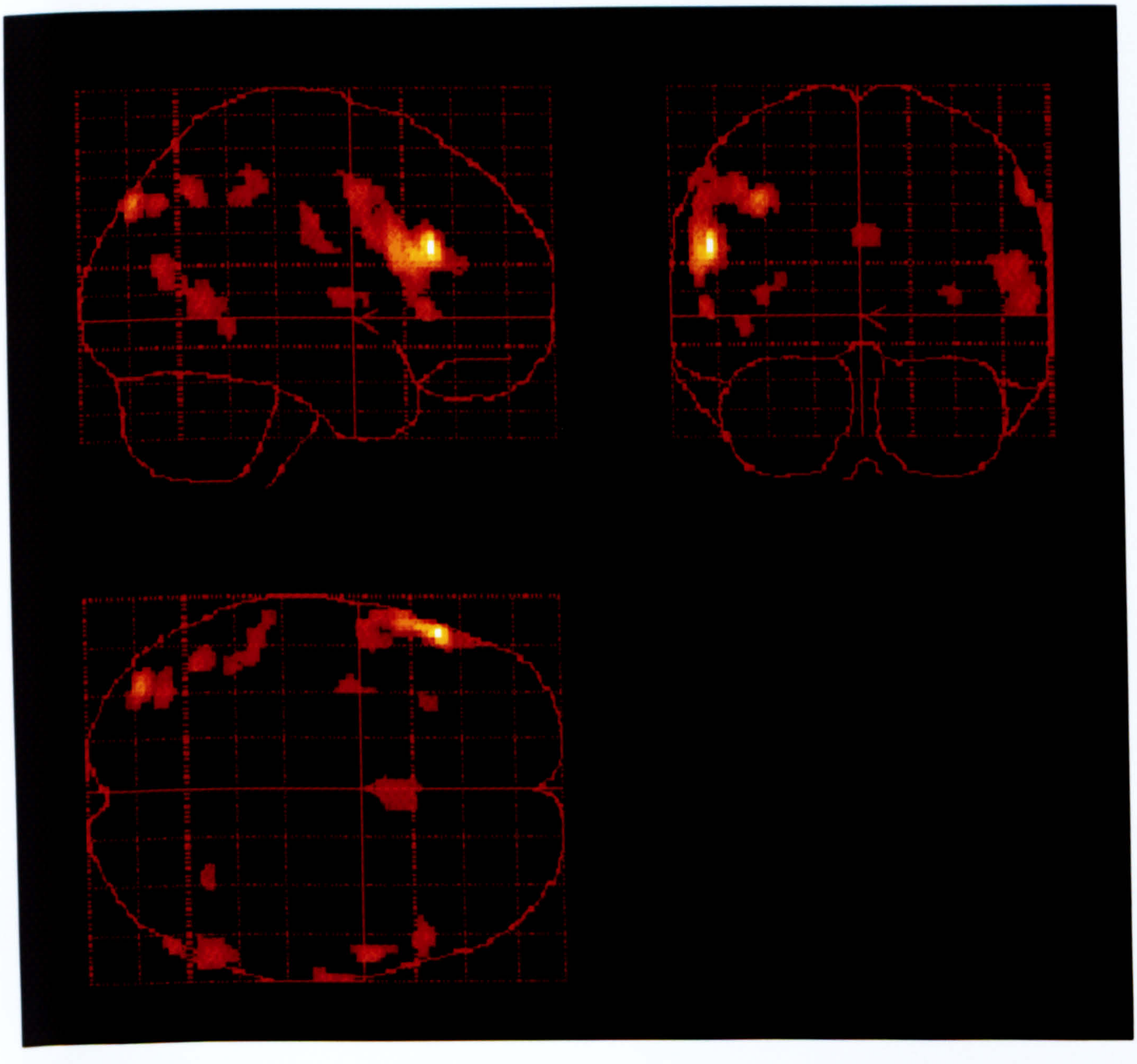


Table 5.3.

Correlation matrix of time series from selected foci

	SMA	R Postcen	R IPL	L STG	L Precen	LIF
SMA						
R Postcen	NS					
R IPL	0.20****	NS				
L STG	NS	NS	NS			
L Precen	0.12***	NS	0.14****	NS		
LIF	NS	NS	-0.08	0.11**	-0.07	

KEY

Pearsons correlation coefficient (2-tailed) **** p<0.0001 *** p<0.001 ** p<0.002

NS– p>0.05

LIF - Left Inferior Frontal gyrus (Talairach x,y,z = -52, 30, 20)

L Precen - Left Precentral gyrus (-38, -8, 30)

L STG – Left Superior Temporal gyrus (-52, -8, 8)

R IPL – Right Inferior Parietal Lobule (54, -48, 40)

R Postcen – Right Postcentral gyrus (64, -16, 40)

SMA – Supplementary Motor Area (4, 6, 58)

Discussion

In this study I examined the neural correlates of covertly articulating the same word at different rates, in order to investigate the relationship between activity in frontal and temporal cortex. While the key difference between the conditions was the rate of covert articulation, one cannot exclude differences in the associated demands on attention and concentration. The subjects reported being able to perform all conditions within the scanning environment, but indicated that they found covert articulation at 60 words per minute to be less demanding than at the slower rates, presumably because the timing of the generation (which was self-paced) at 30 and 15 words per minute was more difficult.

As expected, there was activation of the left inferior frontal gyrus as the rate of covert articulation increased, and this was evident with both the categorical and parametric comparisons. The predicted activation of the left superior temporal gyrus was seen with the categorical, but not the parametric comparison, while both comparisons indicated that faster generation was associated with activation of the right superior temporal gyrus. These data could be interpreted as being consistent with a proposed modulatory effect of left inferior frontal activity on the temporal cortex bilaterally, although we are describing an association and thus it is not possible to be definitive about modulation. Because the paradigm involved covert (as opposed to overt) generation of a single word, it is unlikely that the changes in temporal activation reflected increased semantic or phonological processing, or were secondary to changes in auditory input.

The absence of activation in the left superior temporal gyrus with the parametric analysis may reflect an incorrect assumption that the relationship between the rate of covert articulation and temporal activation would be linear. This would be consistent with the subjects reporting that they found self-pace generation at 15 and 30 words per minute comparably difficult. Even when hearing words presented at different rates, the response in the left posterior temporal cortex differs from that in bilateral and more anterior temporal regions (Price et al 1992). Indeed a post hoc parametric analysis of the present data using a combination of a linear and second order polynomial expansion, as opposed to the linear model, did reveal activity within the left middle temporal cortex and hippocampus with increasing rate.

Both the categorical and parametric analyses revealed an unpredicted activation of the right superior temporal gyrus and the right precentral gyrus at faster rates of generation. The right temporal cortex demonstrates a linear response to increasing rates of overt articulation (Wise et al 1999) and is also deactivated (relative to repetition) during overt verbal fluency (Spence et al 2000). In the absence of substantial *direct* connections between the left prefrontal and right temporal cortex (Pandya and Yeterian 1985; McGuire et al 1991), although it is recognised that the corpus callosum does facilitate trans-hemispheric integration, its activation may be more closely allied to the activation in the right precentral gyrus. The right precentral region we identified is close to an area (52, -6, 41), activated by whispering at a faster rate (Paus et al 1996), and during covert singing (Reiker et al 2000).

The time series data from selected foci indicated that activity in the left inferior frontal and left superior temporal gyri activation were positively correlated. This suggests that the left temporal cortex was activated during the fast rate of verbal generation, rather than being de-activated during the slower rate, as its response was not correlated with that in the other regions that were more activated at the slower rate. Whilst the correlation coefficients are relatively modest in themselves, the relatively large number of observations renders them statistically significant. A positive modulation of left temporal activity during verbal generation accords with data from a PET study of whispering (Paus et al 1996) and reading (Price et al 1996b) at different rates, and electrophysiological studies (Alexander et al 1976; Müller-Preuss and Ploog 1981; Creutzfeldt 1989), but is at odds with data from some PET studies of overt verbal fluency (Frith et al 1995; Friston et al 1991). However, the latter involved the comparison of verbal generation with verbal repetition, and recent evidence suggests that the 'deactivation' of temporal cortex during verbal fluency may be a function of changes in the repetition condition per se (Warburton et al 1996; Spence et al 2000). Verbal fluency also engages semantic and phonological processing to a much greater extent than in the present study.

Considering the results from the categorical and the parametric analyses together, the slower rate was particularly associated with activation in the SMA and the right inferior frontal, superior temporal and inferior parietal cortex, and the left precentral

gyrus. Many of these areas are activated during relatively demanding tasks that entail covert articulation e.g. imagining a sentence being spoken in someone else's voice (Chapter 4). The engagement of these regions during slower rates of verbal generation may thus have reflected greater demands on timing or suppressing a tendency to generate at a faster rate. The SMA, frontal and parietal areas are also activated during the planning, preparation and initiation of voluntary movement (Seitz et al 2000), and are anatomically interconnected (McGuire et al 1991).

While the temporal resolution of fMRI makes it difficult to assess whether temporal cortical activation is secondary to frontal modulation, electrophysiological data in non-human primates and in man suggest that the frontal activity precedes the temporal (Müller-Preuss and Ploog 1981; Creutzfeldt 1989; Alexander et al 1976; Numminen and Curio 1999). Moreover, there are dense connections between these regions that could mediate a direct interaction (Pandya and Yeterian 1985). The findings of the current study are consistent with a frontal modulation of temporal cortical regions during verbal generation, and indicate that this is not simply secondary to increased phonological or semantic processing. As it is evident during the generation of covert speech, it may occur in association with thoughts as well as actions. In the visual system, visual cortical activity is modulated by areas involved in the generation of eye movements (Bahcall and Kowler 1999; Sperry 1950), there is an inverse correlation between the frequency of saccade generation and the magnitude of the visual cortical activation, in the absence of changes in visual input (Paus et al 1995). This may serve to control for the effects of retinal stimulation during eye movements on visual cortical activity. In the somatosensory system, there is greater activation of somatosensory cortex in response to an external stimulus, compared with an identical stimulus that is self-generated (Blakemore et al 1998).

Having identified brain regions normally involved in the generation and monitoring of inner speech, I next sought to examine these processes in patients with schizophrenia, who may be expected to display deficits in verbal self-monitoring. Chapter 6 describes application of the auditory imagery experiment used in Chapter 4 in patients with schizophrenia prone to auditory hallucinations. The experiment in the present chapter was examined in a group of patients with auditory hallucinations in Chapter 7.

Chapter 6

Neural Correlates of Inner Speech and Auditory Verbal Imagery in Schizophrenia

Background

Contemporary cognitive models propose that auditory verbal hallucinations are derived from inner speech that the patient has mis-identified as "alien" through defective self-monitoring (Chapter 1; Frith and Done 1989). This suggests that the functional neuroanatomy of monitoring inner speech may be abnormal in patients who are prone to auditory verbal hallucinations. Auditory verbal imagery, the process of imagining speech, implicitly engages verbal self-monitoring as the subject generates and experiences another person's speech in the auditory modality. While normal inner speech seems to be mainly experienced in the first person (McGuire et al 1995, 1996b), auditory hallucinations in schizophrenia are usually in the second or third person (Nayani and David 1996). The reason for this disparity in grammatical form is unclear but may be important in understanding how auditory hallucinations are derived from inner speech. Clarifying the physiological basis of the relationship between the neural correlates of auditory verbal imagery in the first, second and third person in patients with schizophrenia prone to experiencing hallucinations may shed some light on the brain regions involved in the evolution of AH.

The only previous neuroimaging study of auditory verbal imagery in schizophrenia, which used Positron Emission Tomography (PET), found that remitted schizophrenic patients with a prominent history of hallucinations showed attenuated activation in the left temporal cortex and the rostral supplementary motor area (SMA), compared to both schizophrenics with no history of hallucinations and to healthy volunteers (McGuire et al 1996). In contrast, there were no differences in activation during the generation of inner speech, consistent with the notion that the vulnerability to hallucinations was particularly associated with monitoring of inner speech, which is more engaged during imagery than inner speech.

In this study, I examined the neural correlates of auditory verbal imagery in patients with schizophrenia who had prominent hallucinations, compared with a matched group of healthy volunteers, using fMRI; this permitted a more powerful and sophisticated design

than was previously possible using PET. Subjects performed four tasks; a) The silent articulation of sentences, b) Imagining speech in their own voice (first person imagery), c) Imagining sentences spoken in another's voice, addressed to the subject (second person imagery) and d) Imagining sentences spoken by another about them (third person imagery).

The following hypotheses were tested: -

1. Patients and volunteers would show the same pattern of activation during the generation of inner speech; activation in the left inferior frontal gyrus/insula, corresponding to a common component of silent articulation (Shergill et al 2001, Paulesu et al 1993)
2. Patients, compared to volunteers, would show attenuated activation in the lateral temporal cortices and SMA during auditory verbal imagery, reflecting defective monitoring of more complex inner speech (McGuire et al 1996).
3. Differences in activation between patients and controls would be more pronounced with increased monitoring demand i.e. greater for tasks involving the implicit representation of two people (during third person imagery) compared to one person (second person imagery) (Shergill et al 2001).

Method

Subjects

Eight male patients with schizophrenia according to DSM-IV (one of whom had been involved in the study described in chapter 3), right-handed according to Annett's (Annett 1970) scale, mean age 32 years (standard deviation [s.d.] 10, range 19-47 years) participated in the study. Their mean IQ, estimated with the National Adult Reading Test (NART; Nelson 1991) was 113 (s.d.11, range 94-124). They had experienced prominent and frequent auditory verbal hallucinations during previous exacerbation of their illness, but were in remission at the time of the study, scoring a mean of 24 (range 18-30) on the BPRS (Woerner et al 1988). Control subjects were matched for gender, handedness, age (mean 34 years; s.d. 4; range 27-38 years) and IQ (mean 114; s.d. 8; range 100-120), did not suffer from medical or psychiatric disorders, were not receiving medication, and had no family history of psychiatric disorder.

The patients' clinical profile and history at interview were confirmed by liaison with the responsible clinical team and assessment of medical records. All except one (who was not receiving treatment) had been receiving stable doses of antipsychotic medication for a minimum period of 3 months prior to scanning. Potential subjects were assessed on their ability to perform the experimental tasks (detailed below) outside the scanner. They rated their ability to perform each task on a visual analogue scale and were included if, after training, they consistently scored above 8/10 on this scale on all tasks. After complete description of the study to subjects, written informed consent was obtained.

Tasks performed during fMRI

As described in Chapter 4, subjects listened to single words presented every 3 seconds in a neutral voice that they had previously heard during screening. The words consisted of nouns or adjectives which could readily complete a sentence of the form "I like ....." or "I like being.....". The words were matched for familiarity, frequency of occurrence and imageability across conditions. Each task comprised an "active" and a baseline condition. Before the baseline condition, subjects heard the prompt "now listen", while the "active" conditions were preceded by "imagine". Four "active" conditions were each compared with the same baseline condition. Each task involved 10 alternating 30-second blocks of each condition, lasting a total of five minutes. Task order was counterbalanced across subjects.

Baseline

Subjects were instructed to listen to each word carefully.

Inner Speech

On hearing each word, subjects were asked to silently articulate a sentence of the form "I like....", or "I like being...", ending in the presented word.

First Person Imagery

The instructions were identical to the inner speech condition, except that subjects had to imagine the sentence being spoken in their own voice.

Second Person Imagery

Subjects were asked to complete a sentence in the form "You like....", or "You like being...", ending in the presented word, and to imagine this spoken to them in the voice they had heard during screening.

Third Person Imagery

The instructions were identical to the second person imagery condition, except that the sentence was in the form "He likes....", or "He likes being...", as if spoken about the subject.

After completing each task, subjects rated their ability to perform it as instructed, using a visual analogue scale.

Image Acquisition and Analysis

This was as described earlier in Chapter 4, with an examination of between-group differences using the following one-way analysis of covariance model fitted at each intracerebral voxel in standard space:

$$FPQ_{i,j,k} = :_i + \exists_1 Group_{i,j} + \exists_2 S_{i,j,k} + ,_{i,j,k}$$

Here $FPQ_{i,j,k}$ denotes standardised power at the $_i$th voxel in the $_k$th member of the $_j$th group, $:_i$, denotes the overall mean power, and $,_{i,j,k}$ is a residual quantity. Group is a factor coding for group membership (Control or schizophrenia) and S denotes a vector of measures of subjective rating of difficulty during the imagery task. The null hypothesis of zero between-group difference in mean power of response was tested by comparing the coefficient $\exists_1$ to its non-parametrically ascertained null distribution. To do this the elements of Group were randomly permuted 10 times at each voxel, $\exists_1$ was estimated after each permutation, and these estimates were pooled over all intracerebral voxels to sample the permutation distribution of $\exists_1$. Critical values of a 2-tailed test of size p=0.01 were the 100.(p/2)th and 100.(1-p/2)th percentiles of this distribution (11). Note that this relatively lenient probability threshold was used only to test a restricted search volume comprising those voxels that were generically activated by the task in one or both groups. Comparisons were made between the groups on: - a) each individual task and b) the GBAM's for the three imagery tasks

combined, representing the median activation versus baseline (to identify the correlates of auditory verbal imagery in general).

Results

Auditory Verbal Imagery Ratings

All patients reported that they were able to perform the tasks during scanning. Two controls originally recruited for the study were unable to perform some of the imagery tasks once inside the scanner, reporting that scanner noise made concentration difficult and rating their performance on these tasks as less than 1/10. The data from these subjects were not analysed. There were no between group differences in the subjective ratings for the individual tasks (Figure 6.1). Both groups gave lower ratings for the tasks that involved imagining another person's voice, (second and third person imagery) than those that involved their own voice (inner speech and first person imagery).

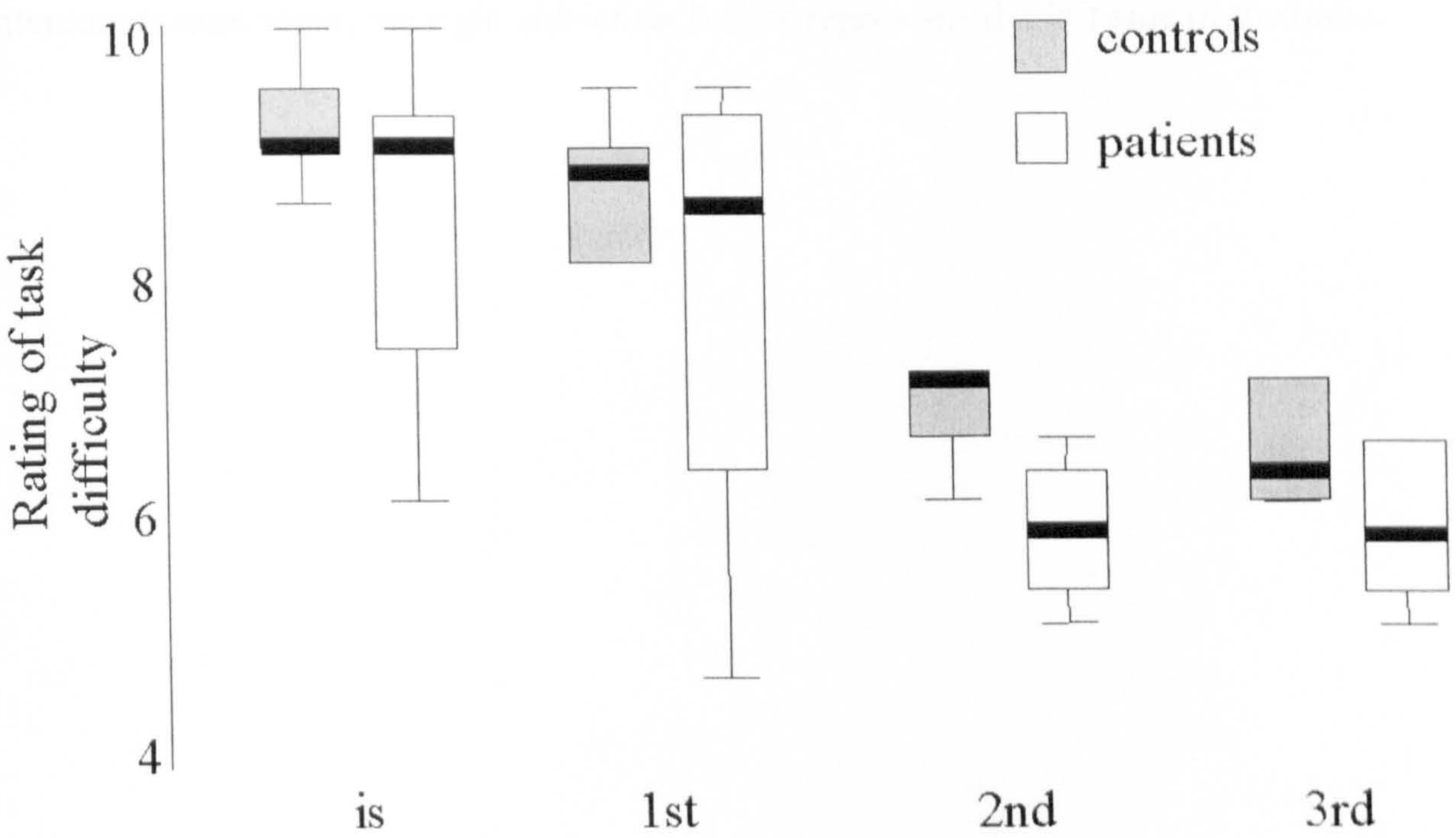
Imaging data – GBAM in controls

The data for the control subjects has been described previously in Chapter 4. To summarise, the inner speech condition was associated with left-sided activation in the inferior frontal gyrus, insula, the junction of the superior temporal gyrus (STG) and inferior parietal lobule, and the superior parietal lobule. Activation was also evident in the supplementary motor area (SMA) and the right posterior cerebellar cortex (Figure 4.1; Figure 6.2). There were responses in phase with the baseline condition in the postcentral gyri, the medial prefrontal and parietal cortex and in the posterior cingulate gyrus. All the areas engaged during inner speech were engaged during the imagery condition (first, second and third person imagery combined), and there were additional right-sided responses in the inferior frontal, precentral and superior temporal gyri, the hippocampus, the thalamus and the inferior parietal lobule (Figure 4.5; Figure 6.2).

Imaging data – GBAM in patients

The inner speech condition, compared to the baseline condition, was associated with left-sided activation in the inferior frontal gyrus, insula, precentral gyrus, the junction of the superior temporal gyrus (STG) and inferior parietal lobule, and the lingual

Figure 6.1 Subjective ratings of auditory imagery tasks in patients relative to controls

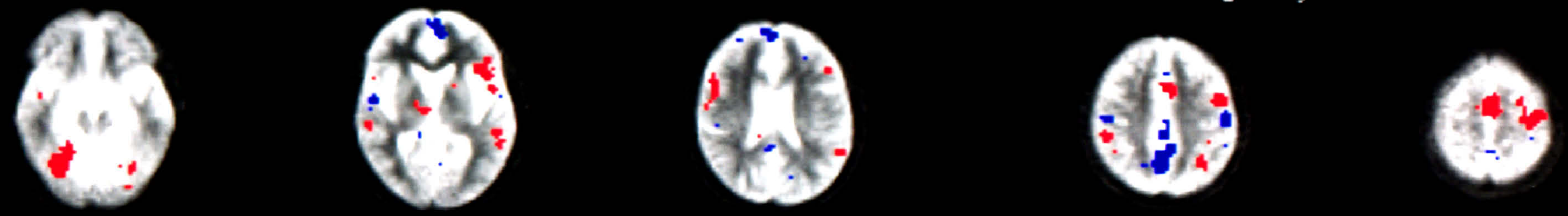


The subjective ratings (scale 0-10), on the vertical axis, for each of the four conditions (on the horizontal axis); inner speech (IS), first person (1st), second person (2nd) and third person (3rd) for patients and controls. Boxplot displaying the mean value (bold line) with 95% confidence intervals (shaded area) and range (whiskers). There were no significant between group differences; IS $t=1.32$, $p<0.25$; 1st $t= 1.14$, $p<0.30$; 2nd $t=1.5$, $p<0.20$; 3rd $t= 1.0$, $p<0.40$.

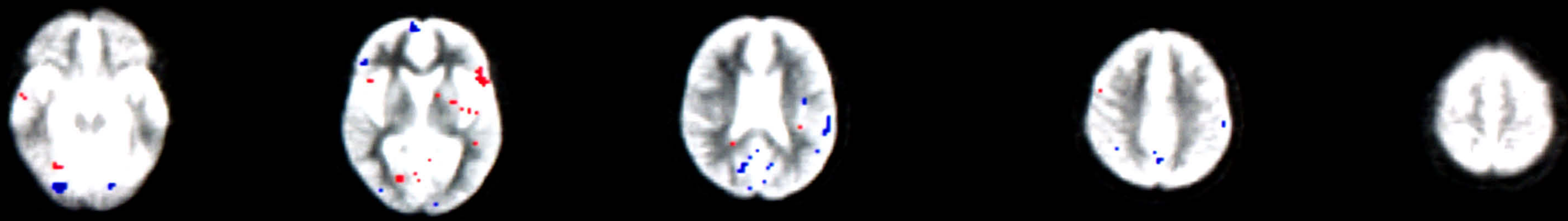
Figure 6.2 Activation during the generation of auditory imagery in patients and controls

Areas showing activation during combined inner speech and first person imagery and combined second and third person imagerytasks in patients and comparison subjects. Activation maps were rendered onto a template in Talairach space. 5 axial slices represent the brain at –13mm, +4mm, +20mm +37mm and +53mm relative to the Intercommisural plane; the right side of each slice represents the left side of the brain.

inner speech and first person imagery

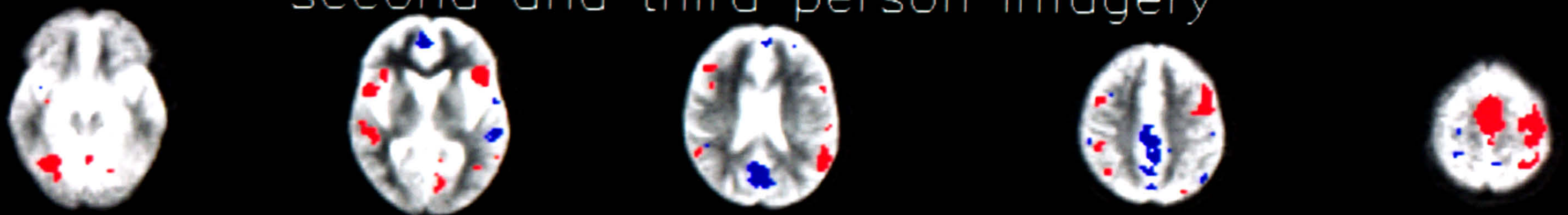


controls



patients

second and third person imagery



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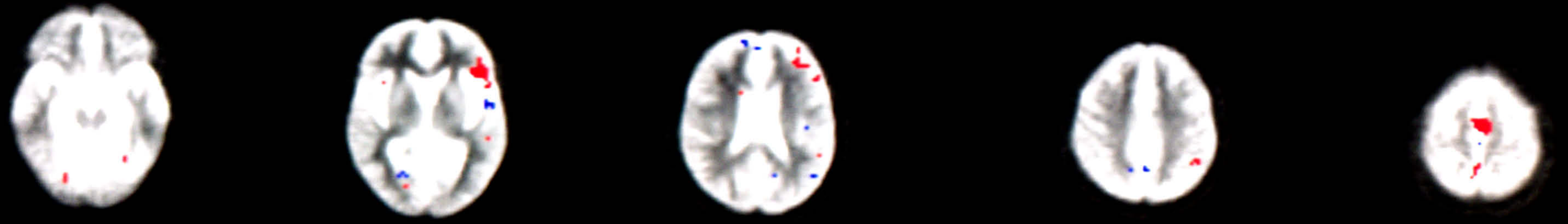

patients

gyrus. Activation was also evident in the supplementary motor area (SMA) and the right posterior cerebellar cortex (Figure 6.2). There were responses in phase with the baseline condition in the medial prefrontal and parietal cortex and in the posterior cingulate gyrus. Imagining first person speech was associated with a similar pattern of activation to inner speech, with additional activation in the right precentral and lingual gyri. Imagining second person speech engaged the areas activated during inner speech plus additional activation in the middle cingulate gyrus with rresponses in phase with the baseline condition evident in the left posterior cerebellum, the anterior cingulate gyrus, the posterior cingulate gyrus and paracentral lobule, the medial parietal cortex and right lingual and fusiform gyri. Imagining speech in the third person was associated with left sided activation in the inferior frontal gyrus, insula, middle frontal gyrus, the pre- and postcentral gyri, STG and the inferior parietal lobule. Further responses were evident in the SMA, bilateral posterior cerebellar cortices and right STG.

During the combined imagery condition (first, second and third person imagery combined) activation occurred in the left inferior and middle frontal gyri, the precentral and postcentral gyri, and the inferior parietal lobule. Midline activation was evident in the SMA, and there were right-sided responses in the precentral gyrus, the lingual gyrus and the posterior cerebellar cortex (Figure 6.2). Responses in phase with the baseline task were evident in the left STG, the medial prefrontal cortex, posterior cingulate gyrus, the cuneus and the medial parietal cortex.

Differences in activation between groups

Only differences significant at $p<0.01$ are reported.

Inner Speech

Patients, compared to controls, showed reduced activation in the right posterior lateral cerebellar cortex, but greater activation in the left insula and right lingual gyrus (Table 6.1).

Imagining first person speech

Relative to controls, patients demonstrated reduced activation in the left insula and middle temporal gyrus, in the posterior cerebellar cortex bilaterally and in the right

Table 6.1 Foci of activation during inner speech in patients relative to controls

REGION	No. Voxels	X	Y	Z	Diff in Mean FPQ	P
<u>Activation during INNER SPEECH</u>	**Patients < Controls**					
R. Posterior cerebellar cortex	8	29	-67	-13	0.4	0.01
	Patients >Controls					
L. Insula	2	-40	14	4	0.3	0.01
R. Lingual gyrus (BA 18)	2	9	-83	-13	0.5	0.001

X,Y,Z refer to the coordinates of maximal response in the atlas of Talairach and Tournoux (1988)

No. Voxels = number of suprathreshold voxels in cluster focussed at this coordinate

L/R left/right

fusiform gyrus, hippocampus and thalamus. Patients also showed attenuated activation of the retrosplenial cingulate gyrus during the baseline task (Table 6.2).

Imagining second person speech

The patients showed reduced activation, relative to controls, in the left fusiform gyrus, the posterior cerebellar cortex bilaterally, and in the right hippocampus and STG (Table 6.3).

Imagining third person speech

Imagining speech in the third person was associated with prominently attenuated activation in the right posterior lateral cerebellum and at two foci in the right superior temporal gyrus in the patients compared to controls. They also showed less activation in the left posterior cerebellum, the thalami bilaterally, and in the right fusiform gyrus and caudate nucleus (Table 6.4).

Auditory Verbal Imagery (first, second and third person imagery combined)

Patients showed attenuated activation in the posterior cerebellum, hippocampal complex, and lenticular nuclei bilaterally, also the right thalamus and middle and superior temporal gyri, and the left nucleus accumbens (Table 6.5; Figure 6.3).

Table 6.2 Foci of activation during first person imagery in patients relative to controls

REGION	No. Voxels	X	Y	Z	Diff in mean FPQ	P
<u>Activation during FIRST PERSON IMAGERY</u>			**Patients < Controls**			
R. Posterior cerebellar cortex	21	26	-67	-13	0.6	0.0005
L. Posterior cerebellar cortex	12	-29	-72	-13	0.4	0.005
R. Hippocampus	10	23	-33	-2	0.4	0.01
R. Fusiform gyrus (BA 37)	9	23	-56	-7	0.4	0.01
R. Thalamus/mamillary body	8	9	-17	4	0.3	0.01
Retrosplenial cingulate gyrus (BA 30)*	5	6	-47	9	0.3	0.01
L. Middle temporal/superior temporal gyri (BA 21/22)	3	-49	-33	4	0.5	0.005
L. Insula	3	-32	14	4	0.3	0.01

Key

* Response greater during baseline condition (a "decrease" during imagery)

Table 6.3 Foci of activation during second person imagery in patients relative to controls

REGION	No. Voxels	X	Y	Z	Diff in mean FPQ	P
<u>Activation during SECOND PERSON IMAGERY</u>		**Patients < Controls**				
L Posterior cerebellar cortex	4	-6	-72	-7	0.4	0.01
L Fusiform gyrus (BA 19)	2	-32	-47	-13	0.3	0.01
R Superior temporal gyrus (BA 42)	2	43	-25	9	0.3	0.01
R Hippocampus	2	26	-33	-7	0.3	0.01
R Posterior cerebellar cortex	1	3	-61	-7	0.4	0.01

Table 6.4 Foci of activation during third person imagery in patients relative to controls

REGION	No. Voxels	X	Y	Z	Diff in mean FPQ	P
<u>Activation during THIRD PERSON IMAGERY</u>		**Patients < Controls**				
R Posterior cerebellar cortex	33	35	-64	-13	0.6	0.0005
R STG (BA 22)	11	46	0	-7	0.4	0.005
R STG (BA 22)	10	49	-28	4	0.4	0.005
L Thalamus	3	-23	-22	9	0.3	0.01
R Fusiform gyrus (BA 19)	3	35	-67	-7	0.3	0.01
L Posterior cerebellar cortex	3	-9	-58	-18	0.3	0.01
R Caudate nucleus	2	14	-11	20	0.4	0.005
R Thalamus	1	20	-17	4	0.3	0.01

Figure 6.3 Activation during the generation of auditory imagery in patients relative to controls

Areas showing attenuated activation during auditory verbal imagery in patients relative to comparison subjects. Activation maps were rendered onto a template in Talairach space. 5 axial slices shown left to right represent the brain at –17mm, -11mm, -6mm, 0mm and +6mm relative to the Intercommisural plane; the right side of each slice represents the left side of the brain. Attenuated activation (coloured red) is evident bilateral posterior cerebellar cortex (Talairach co-ordinates -10, -53, -11 and 20, -47, -11), hippocampi (-24, -28, -6 and 22, -14, -11), lenticular nuclei (-28, -15, 0 and 25, -17, -6) and right middle and superior temporal cortex (43, -10, -11 and 43, -31, 0), thalamus (15, -21, 0) and left nucleus accumbens (-22, -5, -11).

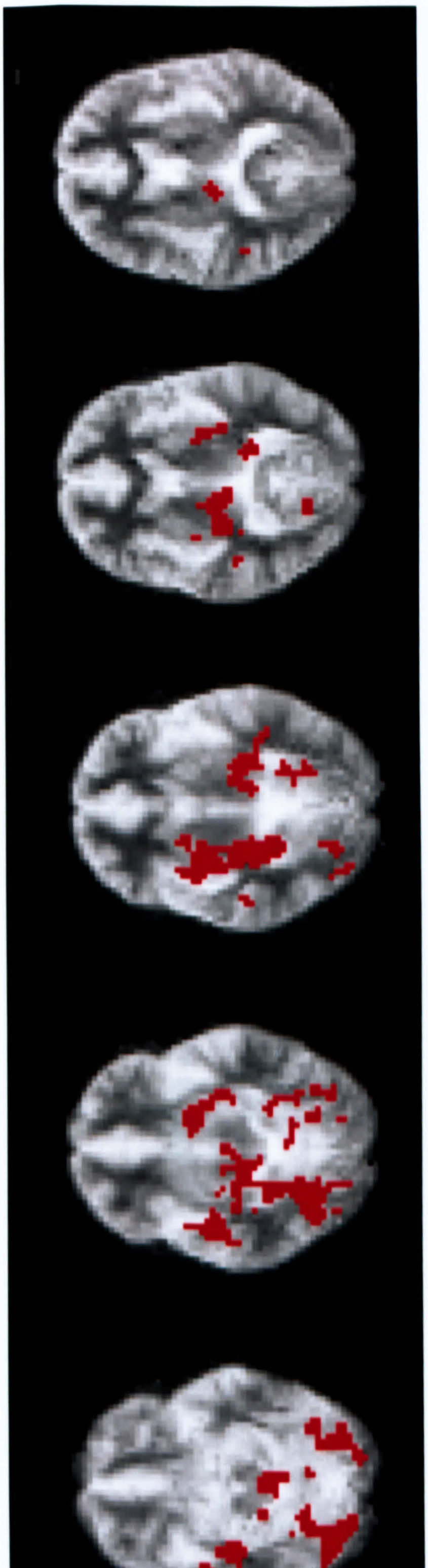

Table 6.5 Foci of activation during combined imagery in patients Vs controls

REGION	No. Voxels	X	Y	Z	P
Activation during COMBINED FIRST, SECOND AND THIRD PERSON IMAGERY					
Patients < Controls					
R Lateral cerebellar cortex	108	20	-47	-11	0.001
L Lateral cerebellar cortex	47	-10	-53	-11	0.001
R Hippocampus	19	22	-14	-11	0.001
L Hippocampus	39	-24	-28	-6	0.01
R lenticular nucleus	97	25	-17	-6	0.001
L lenticular nucleus	13	-28	-15	0	0.001
R MTG (BA 21)	29	43	-10	-11	0.001
R STG (BA 22)	5	43	-31	0	0.01
L nucleus accumbens	32	-22	-5	-11	0.0001

Discussion

Methodology

The overall aim of this study was to use fMRI to identify the neural correlates of inner speech and different forms of auditory verbal imagery in patients with a prominent history of auditory verbal hallucinations. These patients were selected because deficits in these processes may underlie this particular symptom (Chapter 1; Frith and Done 1989, McGuire et al 1996b). One limitation of the study was the failure to include a non-hallucination prone group of patients with schizophrenia, which would have clarified whether the differential activation we observed, was related to the illness in general, as opposed to the propensity to hallucinate. There were no between group differences in ratings of task performance outside the scanner. Ideally functional imaging studies of cognitive tasks should involve the measurement of behavioural performance "on-line", to assess how well subjects are performing during image acquisition. However, auditory verbal imagery is a subjective phenomenon, and as such is not easily amenable to the objective monitoring of performance. I thus sought to minimise the influence of variation in performance by training subjects on the tasks prior to scanning, obtaining ratings of their performance immediately after each task, and excluding those who reported marked difficulties with task execution.

Generation of inner speech

As predicted, the inner speech condition was associated with activation in the left inferior frontal cortex and/or insula in both patients and controls. This suggests the silent generation and articulation of inner speech was not impaired in these patients. This is consistent with similar patterns of activation during an inner speech task in a previous PET study (McGuire et al 1996b) and an absence of behavioural deficits on tasks that entail silent articulation (Haddock et al 1996; Evans et al 2000); supporting the notion that auditory hallucinations are related to defective monitoring, as opposed to generation, of inner speech (Frith and Done 1989, McGuire et al 1996). However, the patients did show an unpredicted attenuation of the right lateral cerebellar cortex. The main task demands were on covert generation and articulation, and this part of the cerebellum has previously been activated in tasks that have implicitly engaged silent articulation (Shergill et al 2001, Warburton et al 1996). The fact that the patients also showed attenuated activation in this region during auditory imagery of another's speech suggests that it was related to increased demands on covert generation and articulation of speech,

(Smith et al 1991, McGuire et al 1996, Shergill et al 2001). The possible contribution of the cerebellum in verbal self-monitoring is discussed in more detail below.

Auditory verbal imagery

The auditory verbal imagery tasks appeared to place greater demands on covert generation and articulation than the inner speech task, because the subjects had to reproduce an internal representation of speech with a particular sound (McGuire et al 1996, Shergill et al 2001); indeed, the subjects rated the imagery tasks as subjectively more difficult than the inner speech task. Imagining speech is thought to entail retrieval of the voice to be imagined from memory and the internal reproduction and "inspection" of the auditory image (Reisberg et al 1991). As predicted, auditory verbal imagery in the patients, as indexed by the three imagery tasks combined, was associated with attenuated activation in the lateral temporal cortex. I particularly expected reduced left temporal activation because this side is classically associated with verbal processing and was the site of differential activation in a previous PET study (McGuire et al 1995). The additional differences in right temporal activation suggest that the putative deficit in verbal self-monitoring may involve impaired processing of the prosody of verbal material; this region is activated when subjects compare melodies with matched non-melodic sequences, make pitch judgments on syllables (Zatorre et al 1992), and assess emotional prosody in spoken sentences (George et al 1996), and right temporal lesions are associated with deficits in processing verbal prosody (Pell et al 1998). The right temporal cortex is also implicated in processing the overall meaning of speech (George et al 1999), so the differential activation may also be related to this aspect of the imagined sentences. Intriguingly this region is particularly active in patients while they report experiencing auditory hallucinations (Chapter 3, Woodruff et al 1997, Dierks et al 1999, Lennox et al 1999). There were no differences between patients and controls in the engagement of the SMA, which was predicted from the attenuated activation evident during imagery in patients in our previous PET study (McGuire et al 1996). The reason for this discrepancy is unclear, particularly as the present study, because it used fMRI, had acquired more images, incorporating around 400 images per individual compared to 12 in the PET study.

There was prominent attenuation of activation in the cerebellum during auditory imagery. While this was unpredicted, data from a PET study of auditory verbal

imagery in schizophrenia showed that hallucination prone patients differed from non-hallucinators in showing less activation in the right posterior cerebellar cortex, although they did not differ from controls (McGuire et al 1996). Data from lesion and neuroimaging studies suggest that the cerebellum may act as a "comparator" in motor acts, comparing the intended with the actual movement and modulating cerebral cortical activity appropriately (Blakemore et al 1998). There is increasing evidence that it may play a similar role in cognitive processing (Desmond and Fiez 1998). Thus the cerebellum may control production of speech or thought in the same way as motor functions, with overt or covert speech analogous to somatic movement. In the case of inner speech, the cerebellum might therefore modulate activity in cortical regions, such as inferior frontal and temporal cortex, much as it does in somatosensory areas during motor acts (Blakemore et al 1998, Leiner et al 1993). The lateral posterior cerebellar cortex receives inputs from the primary and association cortices, via the pons; and projects to the temporal and inferior frontal cortex via the thalamus (Afifi and Bergman 1998). A fMRI study of verbal working memory implicates the cerebellum in computing discrepancies between actual and intended phonological rehearsal, involving the frontal and temporoparietal cortex (Desmond et al 1997). This is consistent with a case report of a patient with right lateral cerebellar damage, which resulted in an inability to correct verbal errors, of which the patient was often unaware (Fiez et al 1992).

I also observed attenuated activation during the auditory verbal imagery, in the right hippocampus, retrosplenial cingulate gyrus and thalamus, which were not predicted. These structures have been associated with memory retrieval (Fletcher et al 1998), and are active during auditory hallucinations in schizophrenia (Chapter 3, Silbersweig et al 1995). Memory function is impaired in patients with schizophrenia and abnormal hippocampal activation has been demonstrated in imaging studies of memory in schizophrenia (Heckers et al 1998), so differential activation at this site may be related to defective recall of speech during auditory imagery. However, the hippocampus is also another region that has been described as the "comparator" in models of cognitive self-monitoring (Gray et al 1991), so the differences at this site, and in the retrosplenial cingulate, could equally be interpreted in terms of defective self-monitoring. A more integrated concept is that of "cognitive dysmetria" as proposed by Andreasen et al (1998), which proposes that schizophrenic symptoms can be understood as a dysfunction

in a network, centered on the prefrontal cortex, thalamic nuclei and the cerebellum. Our data provide some support for this, as they point to functional deficits in some of these regions.

Differences as monitoring demands increase

During third person imagery (compared to activation differences during second person imagery) there was a greater attenuation of the right temporal cortical and right posterior lateral cerebellar activation in the patients, compared to the controls, consistent with the suggestion that these regions are particularly affected by increases in the demand for verbal self-monitoring..

What does imagery tell us about auditory hallucinations?

Overall, these data indicate that patients with schizophrenia who are prone to hallucinations show significantly attenuated activation, when processing inner speech, in several brain regions, including the left insula, right cerebellar cortex, right hippocampus and the lateral temporal cortices. Verbal self-monitoring can occur at two different levels, a) an automatic monitoring of the generation of inner speech and b) an internal "inspection" of the output that is accessible to consciousness (Levelt 1983). Recent psychological studies suggest that auditory hallucinations are associated with deficits at both these levels (Johns and McGuire 1999). The attenuated engagement of the cerebellum, insula and the hippocampus may be more related to impairments at the automatic level of generating and predicting the output, of inner speech, while the differences in temporal activation may be linked to defective "inspection" of that output. This more automatic component of self-monitoring is examined in a different group of patients in Chapter 7, using a less phonologically and semantically demanding task.

Chapter 7

Neural Correlates of Verbal Self-Monitoring in Schizophrenia

Background

In normal subjects, verbal fluency is associated with activation in the left dorsolateral prefrontal cortex (DLPFC) and deactivation (relative to repetition) in the temporal cortex bilaterally (Frith et al 1995, Friston et al 1991). These findings are consistent with the notion that output from regions involved in verbal generation may modulate activation in areas involved in speech perception. Imagining another person's speech implicitly engages both the generation and monitoring of inner speech (Smith et al 1995) and in volunteers is associated with activation in the left inferior frontal cortex, and the temporal, parahippocampal and cerebellar cortex (Chapter 4). Chapter 6 showed that in hallucination-prone patients, imagining speech was associated with normal activation of the left inferior frontal gyrus but attenuated activation of the lateral temporal, medial temporal and posterior cerebellar cortex.

While imagining alien speech engages verbal self-monitoring, it is possible that the activation associated with this process may also be related to the phonological and semantic demands of internally generating a representation of another person's voice (McGuire et al 1996). In the study described in the present chapter, I sought to address this issue by employing a task that did not involve these latter components. Functional magnetic resonance imaging (fMRI) was used to study patients with schizophrenia who were prone to hallucinations while they were covertly generating the same word ("rest") at different rates, as described in Chapter 5. It was expected that increasing the rate of covert articulation would increase the demands on the generation and monitoring of inner speech. Activation during this task was compared in patients with a history of prominent auditory hallucinations and a matched group of healthy volunteers.

On the basis of my previous study of auditory verbal imagery (Chapter 4), I predicted that:

1. Increasing the rate of covert articulation would be associated with activation in the left inferior frontal gyrus, the temporal cortex, and the cerebellum.

2. There would be no differences between patients and comparison subjects in left inferior frontal activation.
3. Patients would differ from comparison subjects in showing attenuated activation in the temporal, parahippocampal and cerebellar cortex.

Methods

Subjects

Eight dextral male patients with schizophrenia (different from those in chapter 6, apart from one subject who was also involved in the study described in chapter 3) participated in the study. Diagnosis was based on DSMIV criteria, using a detailed clinical interview and review of their hospital case notes. Patients were excluded if they had a history of head injury, neurological symptoms, speech or hearing difficulties, fulfilled DSM-IV criteria for abuse or dependence of any illicit drugs or alcohol during their lifetime, or any contraindications to MRI scanning, including metal implants and claustrophobia. They were recruited from wards and clinics at the Maudsley Hospital, London. Their mean age was 31 years (standard deviation [SD] 9; range 20-45 years) with mean IQ 110 (SD 8; range 99-124) They had experienced prominent and frequent auditory verbal hallucinations during previous exacerbation of their illness, but were in remission at the time of the study, scoring a mean of 24 (range 18-32) on the BPRS (Woerner et al 1988). Control subjects were matched for gender, handedness, age (mean 29 years; s.d. 5; range 23-37 years) and IQ (mean 115; s.d. 5; range 110-125), did not suffer from medical or psychiatric disorders, were not receiving medication, and had no family history of psychiatric disorder.

The patients' clinical profile and history at interview were confirmed by liaison with the responsible clinical team and assessment of medical records. All except one (who was not receiving treatment) had been receiving stable doses of antipsychotic medication (5 treated with atypical and 2 with typical antipsychotic drugs) for a minimum period of 4 months prior to scanning. Before inclusion, potential subjects were assessed on their ability to overtly repeat a word at the two rates (once every 1or 4 seconds) to be used during scanning. They proceeded to scanning when they consistently achieved a 1:4 ratio in the number of repetitions timed over a minute. All subjects provided written informed consent to enter the study, which had been approved by the Maudsley Hospital Ethics Committee.

Tasks performed during fMRI

The tasks were generally performed as described in chapter 5, but concentrating on the categorical design rather than parametric design. They are described in brief: -

Fast v Slow Covert Articulation (Categorical comparison).

Subjects covertly generated the word "rest" repeatedly at two self-paced rates (once every 1 or 4 seconds = 60 or 15 words per minute), without speaking. Their accuracy was checked by asking them to tap their finger at the two different rates both prior to and immediately after scanning. During scanning, the two conditions alternated in an ABAB design, with each condition lasting 30 seconds, and 5 cycles of each condition in a 300 second run.

In order to reduce potentially confounding effects of poor performance on activation, only data from subjects who achieved a consistent timing ratio (on finger tapping) of 1:4 between the fast and slow rate, immediately before and after scanning, were analysed.

Image Acquisition

This was described in detail Chapter 5.

Image Analysis

Image analysis was performed on a SPARC Ultra 10 workstation (Sun Microsystems, Palo Alto, CA) using MATLAB (version 5.3, The Mathworks Inc, Natick, MA) and SPM99 software (Statistical Parametric Mapping, The Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm). All data sets were automatically realigned to the first image to correct for head movement, normalised using sinc interpolation and transformed into Talairach space. The transformed data set for each subject was smoothed with a Gaussian filter (Full width half maximum =8mm) to compensate for normal variation in anatomy across subjects. The time series were high pass (126 s) filtered to remove low frequency artifacts.

Categorical Analysis

Statistical analysis was performed for each subject, and the stereotaxically normalised fMRI time series data from all the subjects pooled for group analysis. Analysis of the two-condition task (15 versus 60 words a minute) used a categorical design comparing activation evident during fast greater than slow rate of generation, and vice versa. Cluster level statistics corrected for multiple comparisons were thresholded at $p<0.05$.

Functional connectivity of the left inferior frontal gyrus

An exploratory analysis of the functional connectivity of the left inferior frontal cortex, comparing connectivity between the patient and control groups was also performed. The time series data from the voxel in the left inferior frontal gyrus showing the maximally significant response, in the categorical comparison of covert articulation at one word every 1 and 4 seconds, was selected as a covariate of interest in each individual. The left inferior frontal gyrus was chosen because it is the main region implicated in the generation of inner speech. We sought to identify brain regions whose activity was temporally correlated with that in the inferior frontal gyrus. The SPMs from this analysis were thresholded at $p<0.05$, with voxel level statistics corrected for multiple comparisons.

Between-Group Analyses

Between-group comparisons assessed the significance of differences in the magnitude of each of the above analyses (categorical and connectivity) comparing the patient and control groups, using a random effects model. The random effects model allows the generalisation of the results to the population being sampled, unlike the fixed effects analysis which can only be used to describe the results of individuals within the group. The random effects analysis also guards against the possibility of one subject skewing the results. This second-level analysis compares the mean activation to the inter-subject variation in that activation. If only a few of the subjects show any activation, this will inflate the error variance and reduce the t value. The SPMs were thresholded at $p<0.05$ with cluster level statistics corrected for multiple comparisons, and as the random effects analysis provides a very stringent test (it is recommended to have a minimum of 12-16 subjects per group), we also reported cluster level statistics uncorrected for multiple comparisons in regions included in our a priori hypotheses.

Results

Behavioural Data

All subjects reported that they were able to perform the tasks during scanning and showed a consistent 1:4 timing ratio both pre and post scanning, and there were no differences in performance between the patient and control subjects. Data from all subjects were included in the analysis.

Imaging data – controls

Categorical comparison

The data for the control subjects has been described in detail in Chapter 5 (Tables 5.1 and 5.2). In brief, relative to covert generation at 15 words per minute, covert generation at 60 words per minute was associated with activation in foci in the dorsolateral and the orbital portions of the left inferior frontal gyrus, and in the anterior part of the left superior temporal gyrus. There was also a large area of activation centred on the right precentral gyrus, which included foci in the adjacent postcentral and superior temporal gyri, and a separate activation in the frontal pole. The slower rate of generation was associated with activation in the supplementary motor area (SMA), the left precentral gyrus and the right inferior parietal lobule.

Functional connectivity of the left inferior frontal gyrus

In controls, activity in the left inferior frontal gyrus was positively correlated with activity in the left middle temporal gyrus, inferior parietal lobule, and claustrum. Right-sided correlations were evident in the homologous part of the inferior frontal gyrus, the precentral and postcentral gyri, and the middle temporal and anterior cingulate gyri (Figure 5.3). Activity in the left inferior frontal gyrus was negatively correlated with activity in the left cerebellar cortex and the right thalamus.

Imaging data – patients with history of hallucinations

Categorical comparison

As in the control group, the faster rate was associated with activation in the dorsolateral and orbital portions of the left inferior frontal gyrus, and in the anterior part of the left superior temporal gyrus. Additional activation was evident in bilateral thalami, the right middle frontal gyrus and the SMA. The slower rate of generation

was associated with activation in the parahippocampal gyri bilaterally and the left postero-lateral cerebellum and left inferior occipital gyrus. (See Table 7.1).

Functional connectivity of the left inferior frontal gyrus

Activity in the left inferior frontal gyrus was positively correlated with activity in the left superior temporal gyrus and the right dorsolateral prefrontal, middle temporal and postero-lateral cerebellar cortices. Activity in the left inferior frontal gyrus was negatively correlated with activity in the retrosplenial cingulate and right lingual gyri. (See Table 7.2).

Between- group differences in activation

Categorical comparison

Compared to controls, patients showed reduced activation in a large right-sided region with distinct foci in the superior temporal and postcentral gyri, and the inferior parietal lobule. Attenuated activation was also evident in the right hippocampus and parahippocampal gyrus and in the postero-lateral cerebellar cortex. Patients demonstrated relatively increased activation only in the left lenticular nucleus. (See Table 7.3; Figure 7.1).

Functional connectivity of the left inferior frontal gyrus

Relative to controls, patients demonstrated reduced activation in the right middle and superior temporal gyri, the right insula, a region encompassing the right parahippocampal, inferior temporal and fusiform gyri, and in the precentral gyrus and the medial parietal lobe. Patients did not show greater correlation in any area. (See Table 7.4; Figure 7.2).

Table 7.1 Regions demonstrating significant activation during faster and slower rates in patients (categorical analysis)

REGION	X	Y	Z	Cluster size (No. voxels)	P (cluster)
Greater activation at FASTER rate					
Left inferior frontal gyrus (BA 47)	-52	34	-6	267	0.012
(BA 45/46)	-42	32	12		
Right Supplementary motor area	20	-30	66	521	0.0001
Left Middle temporal gyrus (BA 21)	-52	-12	-8	931	0.0001
Left Superior temporal gyrus (BA 42)	-48	-10	8		
Left Thalamus	-4	-2	6	209	0.03
Right Thalamus	6	-2	6		
Right Middle frontal gyrus (BA 8/9)	58	22	34	735	0.0001
Greater activation at SLOWER rate					
Right Hippocampus/parahippocampal gyrus (BA 36)	30	-20	-22	210	0.03
Posterior Cingulate gyrus (BA 30)	0	-40	12	1352	0.0001
Right Parahippocampal gyrus (BA 27)	8	-36	2		
Left Parahippocampal gyrus (BA 27)	-8	-34	0		
Inferior Occipital gyrus (BA 17/18)	-26	-96	-8	1525	0.0001
Left Posterior lateral cerebellum	-36	-74	-18		

Table 7.2

Regions demonstrating functional connectivity with the left inferior frontal gyrus in patients

REGION	X	Y	Z	Z score	P corrected (voxel)
Positive correlations					
Left Inferior frontal gyrus (BA 45/46)	-54	36	-6	7.1	0.0001
Right Superior frontal gyrus (BA 9)	36	56	28	4.7	0.001
Left Superior temporal gyrus (BA 22)	-60	6	0	4.2	0.01
Right Middle temporal gyrus (BA 21)	54	-14	-12	4.4	0.005
Right Posterior lateral cerebellum	32	-68	-26	4.2	0.01
Negative correlations					
Right Lingual gyrus (BA 17)	10	-96	-10	4.4	0.005
Posterior Cingulate gyrus (BA 29)	2	-40	14	4.3	0.009

FIGURE 7.1 Regions showing between-group differences with increased rate of generation of inner speech.

Cortical regions showing greater activation during increased rate of generation of inner speech (compared to slower rate) in controls compared to patients are shown in red. Activation maps were rendered onto an individual T1 weighted MRI template and coordinates correspond to Talairach space (x,y,z coordinates in mm). The 3 slices, from left to right, represent sections of the brain:- section a is a coronal section at -30mm illustrating differences in activation in the right parahippocampal and superior temporal gyri; section b is a sagittal section at +8mm showing activation in the right lateral cerebellar cortex and section c is an axial section at +16mm showing activation in the right superior temporal gyrus.

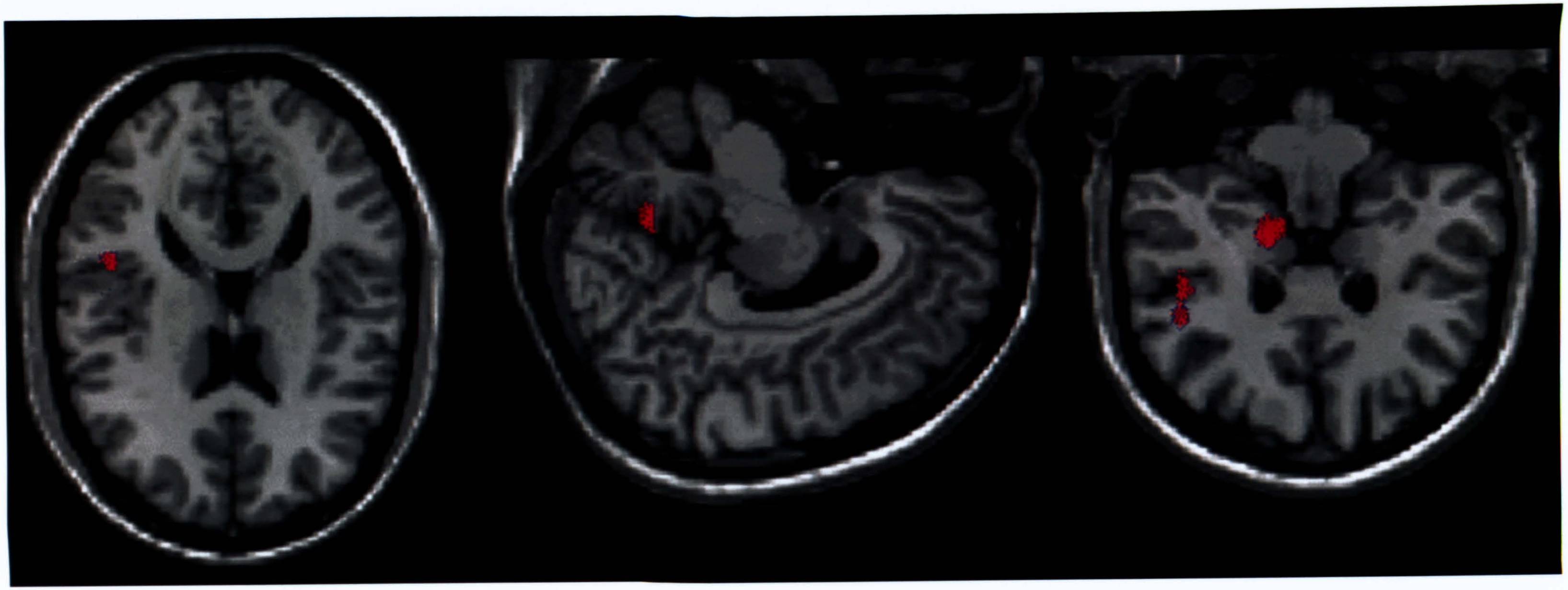

Table 7.3

Patients Vs Controls - Differences during faster and slower rates (categorical analysis)

REGION	X	Y	Z	Cluster size (No. voxels)	P (cluster)
Greater activation in patients during FASTER rate					
Left Lenticular nucleus	-22	-2	6	669	0.001
Greater activation in controls during FASTER rate					
Right Postero-Lateral Cerebellum	8	-62	-8	361	0.007 *
Right Parahippocampal Gyrus (BA 27)	16	-30	-2	157	0.05 *
Right Postcentral Gyrus (BA 1,2,3)	58	-18	34	822	0.0001
Right Inferior Parietal Lobule (BA 40)	58	-24	24		
Right Superior Temporal Gyrus (BA 42)	50	-32	16		

* uncorrected for multiple comparisons

FIGURE 7.2 Regions showing between group differences with increased rate of generation of inner speech – Connectivity analysis.

Cortical regions showing increased correlation with activation of the left inferior frontal gyrus in controls compared to patients are shown in red. Activation maps were rendered onto an individual T1 weighted MRI template and coordinates correspond to Talairach space (x,y,z coordinates in mm). These 3 slices (not corresponding to those in Figure 7.2) from left to right, represent sections of the brain:- section a is a coronal section at -14mm illustrating differences in activation in the right insula and precentral gyrus; section b is a sagittal section at +44mm showing activation in the right insula, parahippocampal and superior temporal gyri and section c is an axial section at -16mm showing activation in the right parahippocampal gyrus and the right superior temporal gyrus/insula.

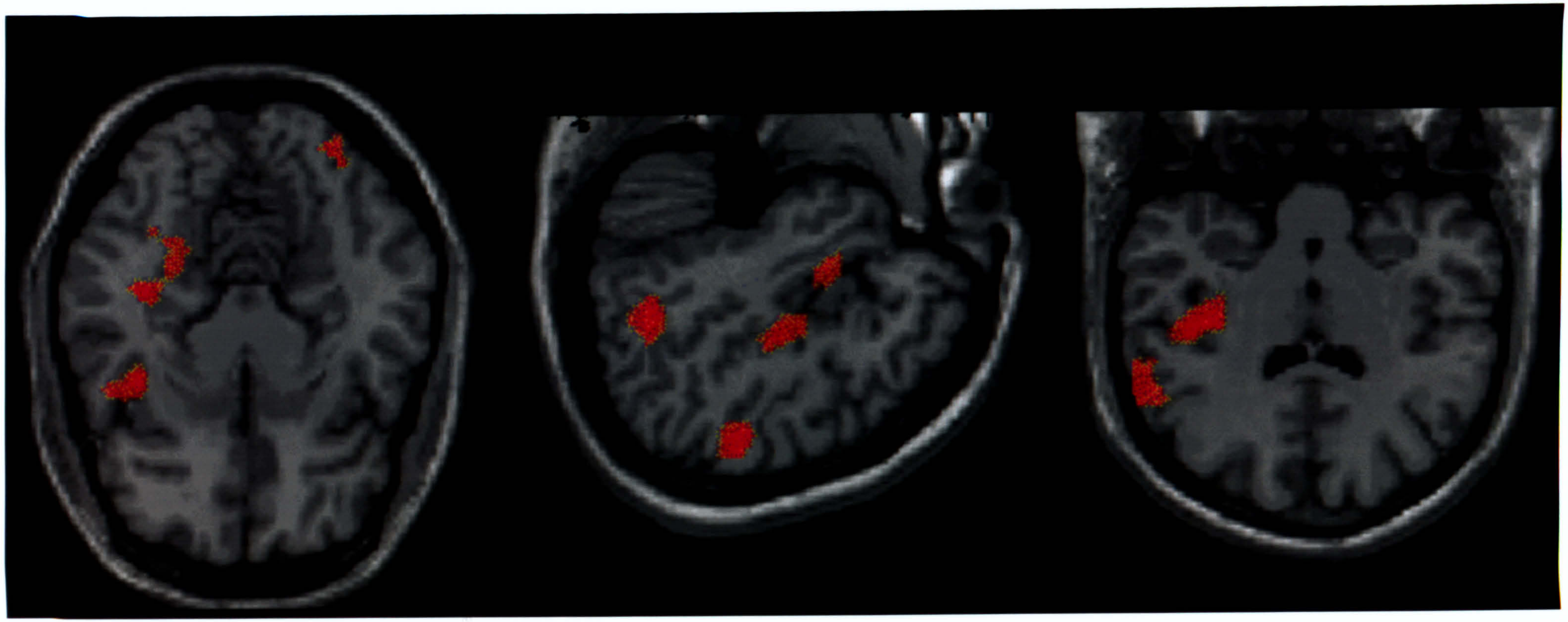

Table 7.4

Patients Vs Controls - Differences in functional connectivity with the left inferior frontal gyrus

REGION	X	Y	Z	Cluster size (No. voxels)	P (cluster)
Correlations greater in controls					
Right Parahippocampal/Fusiform Gyri (BA 36/ 37)	40	-30	-16	1689	0.0001
Right Insula	44	-14	10	340	0.01 *
Right Precentral Gyrus (BA 4/6)	66	-8	32	699	0.001
Left Medial Parietal Lobe (BA 7)	-16	-78	56	716	0.001
Right Superior Temporal Gyrus (BA 22/38)	44	0	-10	194	0.05 *
Right Superior/Middle Temporal Gyrus (BA 22/21)	52	6	-16		

Discussion

Methodology

The main aim of this study was to use fMRI to examine the relationship between activity in cortical regions involved in generating and monitoring inner speech in patients with a history of auditory verbal hallucinations. These patients were selected because deficits in these processes may underlie this symptom in schizophrenia (Chapter 1; Frith and Done 1989, McGuire et al 1996). One potential limitation of the study was that we did not include a group of patients with schizophrenia who were not prone to auditory hallucinations. This might have clarified whether the differential activation we observed was related specifically to the propensity to hallucinate, as opposed to the disorder of schizophrenia. There were no between group differences in ratings of task performance outside the scanner. Ideally, functional imaging studies of cognitive tasks should involve the measurement of behavioural performance "on-line", to assess how well subjects are performing during image acquisition. However, covert speech cannot easily be measured without introducing additional and potentially undesirable cognitive operations. I sought to minimise the influence of variation in performance by training subjects on the tasks prior to scanning, obtaining ratings of their performance immediately after each task, and excluding those who reported or demonstrated marked difficulties with task execution.

Inner Speech

As predicted, increasing the rate of covert articulation was associated with activation in the left inferior frontal cortex. This was evident in all subjects, both patients and controls and suggests that the silent generation and articulation of inner speech was not impaired in patients with a history of hallucinations, consistent with findings from previous neuroimaging and cognitive psychological studies (Chapter 4, McGuire et al 1996).

Verbal Self-monitoring

The anticipated activation of the lateral temporal cortex in association with the faster rate of generation was evident in the healthy controls. Relative to controls, the patients showed a significant attenuation of activation in the right (but not the left) superior temporal gyrus, the right parahippocampal gyrus and the right cerebellar

cortex. These data are consistent with a modulatory effect of left inferior frontal activity on activity in the temporal, parahippocampal and cerebellar cortex in healthy subjects, which is attenuated in patients with schizophrenia who are prone to auditory hallucinations. In my previous fMRI study of auditory verbal imagery, I found similar differences between hallucination-prone patients and controls in these three areas (Chapter 6, Shergill et al, 2000b). Because the paradigm in the present study involved the covert generation of a single word in the subject's own 'inner voice' (as opposed to a meaningful sentence in someone else's voice), it is unlikely that the differential activation in the two groups in this study was related to semantic or phonological processing. The involvement of the right, as opposed to the left, temporal cortex is of particular interest, as the right temporal cortex has also been a site of differential activation in studies of verbal fluency in schizophrenia (Spence et al 2000), and this region appears to be more active than its left homologue when patients are experiencing auditory hallucinations (Chapter 3, Woodruff et al 1997, Dierks et al 1999, Lennox et al 1999).

A common feature of lateral temporal, parahippocampal and cerebellar cortices is that they are all implicated in cognitive self-monitoring (Frith et al 1992, Gray et al 1991, Blakemore et al 1998), and more specifically in the monitoring of inner speech (Chapter 6). It has been proposed that verbal self-monitoring can occur at two different levels, a) an automatic monitoring of the generation of inner speech using information derived from a corollary discharge b) an internal "inspection" of the output that is accessible to consciousness (Levelt et al 1983). Finding the same pattern of differential activation in hallucinators and controls with this paradigm and with auditory verbal imagery suggests that these differences could be entirely accounted for by a deficit in the more 'automatic' form of self-monitoring. One exception may be the left temporal region, which only differentially engaged during auditory verbal imagery. Differences in this region may thus be related to the more conscious 'inspection' of inner speech. The robust nature of these findings is illustrated by the fact that they were evident despite different cognitive paradigms, different subject samples, and the use of different methods of fMRI analysis.

Functional connectivity of the left inferior frontal gyrus

The functional connectivity analyses generated maps of regions that showed BOLD activity that was significantly correlated with that in the maximal focus of activation within the left inferior frontal cortex, over the course of the experiment. This provided a more stringent temporal test of our hypotheses than the categorical comparison, and demonstrated that the correlation between activity in the left inferior frontal and the temporal and cerebellar cortices in controls was positive. A positive modulation of temporal activity during verbal generation accords with data from a PET study of whispering (Paus et al 1996) and reading (Price et al 1996) at different rates, and electrophysiological studies (Alexander et al 1976; Müller-Preuss and Ploog 1981; Creutzfeldt 1989), but is at odds with data from some PET studies of overt verbal fluency (Frith et al 1995; Friston et al 1991). However, as discussed in chapter 5, the latter involved the comparison of verbal generation with verbal repetition, and recent evidence suggests that the 'deactivation' of temporal cortex during verbal fluency may be a function of changes in the repetition condition per se (Warburton et al 1996; Spence et al 2000).

In the patients, relative to control subjects, left inferior frontal activity was less strongly correlated with activity in the right superior and middle temporal gyri, and the junction of the right parahippocampal/fusiform gyri. The attenuation of the correlation between activity in the left inferior frontal and right temporal cortex is consistent with the results of the categorical comparison discussed above, while the difference in the parahippocampal/fusiform region was close (but lateral) to the parahippocampal site of differences in the categorical comparison.

What does self-monitoring tell us about auditory hallucinations?

Overall, these data indicate that patients with schizophrenia who are prone to hallucinations show significantly attenuated activation when processing "simple" inner speech, in the right cerebellar cortex, right hippocampus and the right lateral temporal cortex. This supports the notion that psychotic symptoms such as auditory hallucinations are related to impaired monitoring of inner speech, and that this monitoring deficit is associated with a functional dysconnectivity between brain areas that generate and monitor inner speech. Moreover, this study suggests that attenuated engagement of the cerebellum and the hippocampal region may be particularly related

to impairments at the automatic level of generating and predicting verbal output, while the abnormalities in left temporal activation may be more related to impairments at the level of "inspection" of that output. This would be consistent with data showing that attending to auditory stimuli is particularly associated with increased activation in lateral temporal cortex (but not the cerebellum or hippocampus) (Woodruff et al, 1996).

Chapter 8

Conclusions

Auditory verbal hallucinations are perplexing phenomena that occur frequently during psychosis and account for a significant amount of distress among patients with psychotic disorders. There has been widespread interest in their aetiology and pathophysiology, and over the last century various cognitive models of hallucinations have been proposed. Functional neuroimaging has allowed us to examine some aspects of these models in a relatively non-invasive manner. Within this field, functional magnetic resonance imaging provides a more powerful means of examining the brain activity associated with cognitive processing than is possible with SPET and PET, which involve the acquisition of fewer images, exposure to radioactive substances and offer a poorer spatial resolution. Concurrent improvements in analytical methods and computing power have also made it possible to examine activity in the entire brain, as opposed to few regions of interest. This thesis has sought to clarify the neural substrate of auditory hallucinations in schizophrenia, and to examine the cognitive processes implicated in theoretical models of the disorder, especially language processes. The objective was to clarify the neurocognitive mechanisms underlying auditory hallucinations and thus provide a scientific basis for their treatment, with, for example, cognitive psychological strategies (Shergill et al 1998) or transcranial magnetic stimulation (Hoffman et al 2000).

Neural substrates of auditory hallucinations and language

One implication of the work in this thesis is that auditory hallucinations probably arise through a disorder of language processing. It also indicates that hallucinations are unlikely to arise from a focal lesion, along the lines of a typical neurological-deficit model. Leaving aside the methodological issues, which I will discuss further below, some consistent findings that emerged were: -

1. Healthy subjects showed activation in brain regions involved in speech generation (left inferior frontal cortex) and perception (temporal cortex) during the generation and inspection of inner speech. Increased demands on monitoring were associated with increased activation within the lateral temporal cortex bilaterally and in the right posterior lateral cerebellum.

2. Healthy subjects demonstrated positive functional connectivity between the left inferior frontal cortex and the lateral temporal cortex bilaterally during the generation of even simple inner speech.

3. The perception of auditory hallucinations was associated with activation in brain regions that are normally engaged during both the generation and perception of inner and overt speech (the frontal and temporal areas described above). Within the lateral temporal cortex there was greater activation in the right hemisphere than the left.

4. The perception of auditory hallucinations was *not* associated with activation in the cerebellum, the supplementary motor area or the right parahippocampal region

5. When generating inner speech, patients with schizophrenia who were prone to developing hallucinations showed relatively reduced activation in the right lateral temporal cortex, the right lateral posterior cerebellum and the right parahippocampal region, areas implicated in cognitive self-monitoring.

Overall, the results are consistent with the notion that auditory hallucinations arise through a disruption of normal cognitive processes, such as the monitoring of self generated verbal material (Frith 2000). Self-monitoring is of fundamental importance to normal cognitive function, as the brain needs to have a mechanism for planning and controlling motor acts and their consequences. A "feed forward" model has been shown to be an important component of this mechanism (Wolpert et al 1995). This allows the motor outflow (plan) to generate an efferent copy that serves to anticipate and cancel out the sensory effects of the motor act. The model allows for the fact that information relying on sensory feedback is too slow to control rapid movements, and that mental practice can enhance actual movements. The operation of efference copy has been demonstrated in the visual system (Sperry 1950). Sperry noted that surgical rotation of the eye in fish was followed by circling behaviour; he proposed that any pattern of activity that will normally cause a displacement of the visual image in the retina, must have a corollary discharge to visual centres to compensate for the retinal displacement. He went on to give the example that when one moves the eyes normally, the world is experienced as stable, despite the succession of images passing the retina. However, when the eye is moved passively, such as by tapping the eyeball, the visual world seems to move. This simple cancellation theory was superceded by the concept of feed forward control, in which motor commands are monitored as they

occur, prior to any movement. In the somatosensory system, there is greater activation of somatosensory cortex in response to an external stimulus, compared with an identical stimulus that is self-generated (Blakemore et al 1998). In schizophrenia, a failure of the internal model has been suggested to underlie some psychotic symptoms (Frith et al 2000).

On the basis of the main findings from this thesis (listed above) one could postulate a neurophysiological model where the neural substrate of generating inner speech would be the left inferior frontal gyrus, whilst monitoring of self-generated inner speech would involve the lateral temporal cortices, the right parahippocampal region and the right lateral cerebellar cortex. The data from this thesis also suggest that this monitoring function may be subdivided into an automatic "corollary discharge" type monitoring, involving the right hippocampal complex and cerebellum, and a more "conscious" inspection component, involving the lateral temporal cortex. This raises the question of whether this putative failure of self-monitoring in schizophrenia is unique to verbal thoughts or is also apparent during other complex motor acts, either in planning or during their execution. If overt speech and inner speech can be regarded as complex motor acts, this would then lead to the prediction that other self-generated motor acts would also be affected by dysfunctional self-monitoring, perhaps leading to other psychotic experiences, such as passivity phenomena. This could be examined in an analogous way to the experiment described in Chapter 5, using a parametric design with motor (as opposed to inner speech) tasks and experimentally manipulating monitoring load.

In summary, applying a conventional corollary discharge model, left inferior frontal activation during the generation of inner speech would normally modulate activation in the lateral temporal cortex through comparators like the parahippocampal region and cerebellum. During auditory hallucinations one would then predict the presence of left inferior frontal activation (related to inner speech generation), an absence of cerebellar and parahippocampal activation (reflecting a failure of self-monitoring) but increased activation in the lateral temporal cortex (due to a failure of modulation); this is what was observed in the study described in Chapter 3.

However, this raises other questions that relate to wider issues such as the characteristics of spontaneous inner speech. Normal inner speech is thought to be largely neutral and first person in form (Hulbert et al 1994). In contrast, auditory hallucinations in schizophrenia are most commonly experienced in the second person and are derogatory or hostile (Nayani and David 1996). The study in chapter 4 attempted to examine the neural structures that might be involved in this apparent transformation from first person to second or third person speech and identified the cerebellum and temporal cortex as candidate regions. Both showed abnormal activation in patients who were prone to developing hallucinations but differential engagement (activation within temporal cortex, but not cerebellum) when patients were actually hallucinating. The suggestion is that these may be key structures in a network of areas normally responsible for verbal self-monitoring and while attenuated activation in one region may not be sufficient to precipitate hallucinatory activity, if allied to changes within another node, such as the supplementary motor area or hippocampus this may be sufficient to precipitate AH.

There is clearly a need for a more detailed examination of normal inner speech; its form, content and when it is (or is not) accessible to awareness. This could be done through a psychological examination of inner speech in a large sample of normal individuals, those prone to disorders such as schizophrenia, and in patients with hallucinations. It may be that the form and content of inner speech is similar in these two groups, but the awareness and/or appraisal of this activity is different. Thus, patients may be less (consciously) aware of their inner processes, while normal subjects may be better able to keep (conscious) track of these. It would therefore be easier for patients to fail to recognise their inner thoughts as their own. Equally, the distinction may be with how the same form of internal material or events are appraised by the individual. These possibilities could be investigated by asking subjects to record their spontaneous thoughts each time a randomly generated cue is heard at intervals during the day. The neural correlates associated with these experiences could be examined using the sampling approach described in chapter 3.

It has previously been noted that AH in patients are prominently negative in content (Nayani and David 1996), but this does not appear to be the case in normal individuals who report the experience of hearing voices (Bentall and Slade 1985b).

Following on from this, it would be useful to examine the affective valence of auditory hallucinations; it has been suggested that inner speech is perceived as hallucinations on the basis that the content is hostile and affectively not ego-syntonic (Johns & McGuire, 1999). However, patients with obsessive-compulsive disorder can have markedly ego-dystonic thoughts that are not experienced as auditory hallucinations. The neural correlates of these phenomena could be compared, again using the fMRI sampling technique; contrasting hostile with neutral or pleasant hallucinatory utterances, and voices with intrusive thoughts.

While fMRI has provided details of the anatomical structures within the brain that are associated with hallucinations, the sequence in which different regions are engaged over the course of a hallucinatory event is still unclear. This issue is difficult to address using fMRI because the temporal resolution is insufficient to distinguish small differences in timing (of the order of milliseconds). However, electroencephalography (EEG) is a technique with a significantly better temporal resolution, and this can be combined with fMRI, such that both forms of data are collected simultaneously while the subject is in the scanner. This can ally the high temporal resolution of EEG with the relatively high spatial resolution of neuroimaging (Goldman et al 2000). However, there are considerable technical problems with having additional magnetic equipment in the MRI environment, making such studies logistically demanding. Magnetoencephalography (MEG) is another technique with high temporal resolution, but it is not yet possible to perform MEG and MRI examination at the same time due to equipment incompatibility. However, MEG and fMRI data could be acquired within a short space of time of each other and integrated post-hoc.

A further unresolved issue is the strength or weakness of association between different regions within the network associated with hallucinations. This functional connectivity (or dysconnectivity) is a crucial aspect of the self-monitoring process and it would be useful to examine this more formally using mathematical modelling techniques, such as path analysis (Bullmore et al 2000). One could select a simple verbal generation task, such as that used in Chapters 5 and 7, increase the demands on verbal processing in a parametric fashion with a large number of increments and examine the relationship between activity in inferior frontal, temporal,

parahippocampal and cerebellar cortex using path analysis. This may clarify the strength of associations between different "nodes" of the network. However, both the connectivity and EEG/MEG studies suffer from not being able to provide a unique solution for any given set of results; i.e. that the same set of observations can arise by activity within several different combinations of brain regions. One way of overcoming these limitations is to determine a clear *a priori* hypotheses about the regions likely to be involved; the work in the thesis provides the basic neuroanatomical framework necessary for this, constraining the number of parameters to a manageable number. Another more direct way of investigating inter-regional connectivity is to use diffusion tensor imaging to visualise the anatomy of the white matter tracts that link these areas. This may clarify whether the functional dysconnectivity associated with hallucinations is related to an underlying anatomical change.

Methodological limitations

A methodological limitation applicable to all the work in this thesis is the use of small numbers of subjects. Ideally, one would like the number of subjects to be larger to allow the results to be more generalisable. However, whilst the main constraint on recruiting normal subjects is the relatively high cost of fMRI, with patients there is the additional problem of finding subjects with the appropriate symptoms who are willing and able to tolerate a scanning session. The studies in this thesis required the recruitment of psychotic patients who were either experiencing hallucinations that were frequent yet intermittent, or had a strong history of such symptoms, were willing to lie in a narrow, claustrophia-inducing space for at least an hour, and were able to cooperate with relatively demanding experimental paradigms. In practice, it takes a great deal of time to collect a group of such subjects. I attempted to compensate for the limitations of small numbers by using fMRI to acquire a large number of images in each subject. I also used more than one task, or imaging technique, in each subject. This allowed me to study the same cognitive process in the same individual using different methods.

Implications for treatment

How can this work inform us about possible clinical strategies to ameliorate auditory verbal hallucinations? It is instructive to examine the psychological strategies that

patients themselves employ to cope with auditory hallucinations (see Table 8.1). The most common strategies can be categorised as:- 1) Distracting activities, such as listening to music or seeking other people to talk to; 2) Behavioural tasks, such as relaxing, sleeping or taking exercise; 3) Cognitive tasks, such as ignoring, blocking out, or switching thoughts to other areas. Both talking and listening to speech engage the brain regions involved in generating and perceiving language; areas that are activated during auditory hallucinations, and the effectiveness of these activities may reflect a competition with AH for shared neural resources, an idea based on the effects of concurrent AH on the neural response to exogenous speech (Woodruff et al 1997). It follows that the more complex and meaningful the demands on auditory-verbal processing, the greater the engagement of language processing areas and the stronger the competition. Thus holding a conversation (which involves speaking and listening) seems to be generally more effective in attenuating the severity of AH than passively listening to speech. The effectiveness of behavioural tasks, and to some extent the cognitive strategies, would appear to be related to switching of attentional resource away from language related areas – again something that would lead to a reduction in speech related areas. The cognitive strategies per se would depend largely on what was actually being done to ignore the "voices" or what one was switching one's thoughts to and would include elements of both the earlier strategies.

My colleagues and I have used some of the above techniques in a clinical setting, in patients with treatment-refractory auditory hallucinations, with some initial promise. We have also employed two novel strategies, derived from the work in this thesis, which some patients have reported as being useful. These are deliberate generation of auditory verbal imagery of a voice that is well known to the patient (to 'compete' with auditory hallucinations for common temporal cortical resources; demonstrated in Chapter 4) and deliberate generation of visual imagery (on the basis that shifting attention to the visual modality would serve to reduce activity within auditory areas (Haxby et al 1994, Chapter 4). It is too early to say whether these are effective, but the plan is to incorporate these types of strategies, in a treatment package, to provide some initial control over the hallucinatory experience and this is used to engage the

Table 8.1

Strategies used by patients in coping with Auditory Hallucinations

STRATEGIES	F (1981) (n=40) %	R (1991) (n=186) %	O (1994) (n=40) %	C (1996) (n=100) %	N (1996) (n=100) %
Listening to music	73	-	38	58	30
Relaxing/sleeping	73	-	43/45	48/53	43
Speaking with someone	48	-	50	57	63
Distracting thoughts	73	24	-	48	39
Lying or walking	63	-	40	-	23
Physical exercise	55	24	-	49	13
Medication	53	-	48	44	-
Ignoring AH	-	52	38	40	-
Prayer/meditation	-	-	43	43	-

KEY
F= Falloon (1981); all outpatients; all diagnosis schizophrenia
R= Romme (1992); questionnaire to TV audience; 41% response rate
O= O'Sullivan (1994); depot clinic attenders; 88% schizophrenia
C= Carter D. (1996); 69% in-patients; 67% schizophrenia
N= Nyani (1996); 55% in-patients; 61% schizophrenia

patient in a more critical appraisal of their experiences, following a more standard cognitive behavioural treatment model.

A more direct method of treatment directly utilising the data from the studies described in the earlier chapters is Trans-Cranial Magnetic Stimulation (TCMS). This has been mainly used for treating depression, but there is some data demonstrating its efficacy in treating AH (Hoffman et al 2000). The technique itself requires an electromagnetic to be placed on the scalp to generate an electrical field that passes through the scalp and skull to induce corresponding changes in the electrical fields and neuronal activation in underlying cortex. Studies demonstrate that low frequency (below or at 1 hertz), extended duration (circa 15 minute) repetitive TCMS produces sustained reductions in activity within the stimulated brain regions, as well as other functionally connected brain areas. A TCMS study from Yale University (Hoffman et al 2000) has shown an effect in a group of 12 patients (TCMS given over the left temporal region) only in those patients not taking anticonvulsants, and only when the TCMS was given over the longer period of stimulation (12 or 16 minutes). This study found that patients tolerated TCMS without difficulty, except for some transient complaints of headache. A key issue with TCMS is where to site the probe for optimal effect – and functional magnetic resonance imaging (fMRI) provides a scientific basis for this. On the basis of the results of chapters 3-7, the right temporal cortex may be the optimal site for TCMS and I am currently involved in a study examining this hypothesis.

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Publications Arising from Thesis

- Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Shergill SS, Brammer MJ, Williams S, Murray RM, McGuire PK. *Archives of General Psychiatry* 2000;57(11):1033-1038.

- The functional anatomy of auditory verbal imagery in patients with auditory hallucinations. Shergill SS, Bullmore ET, Simmons A, Murray RM, McGuire PK. *American Journal of Psychiatry* 2000; 157: 1691-1693.

- A functional MRI study of Auditory Verbal Imagery. SS Shergill, ET Bullmore, MJ Brammer, SCR Williams, RM Murray, PK McGuire. *Psychological Medicine* 2001; 31: 241-253.

- Modulation of activity in temporal cortex during generation of inner speech SS Shergill, M Brammer, R Fukuda, E Bullmore, RM Murray, PK McGuire. Submitted *Human Brain Mapping*.

- Attenuated Engagement of Brain Areas That Mediate Verbal Self-Monitoring in Patients With Auditory Hallucinations. SS Shergill, M Brammer, R Fukuda, S Williams, RM Murray, PK McGuire. Submitted *American Journal of Psychiatry*.